

# EXHIBIT H

**IN THE UNITED STATES DISTRICT COURT  
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA  
CHARLESTON DIVISION**

<b>IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION</b>	<b>Master File No. 2:12-MD-02327 MDL 2327</b>
<b>THIS DOCUMENT RELATES TO:  ALL CASES LISTED BELOW</b>	<b>JOSEPH R. GOODWIN U.S. DISTRICT JUDGE</b>

<i>Mullins, et al. v. Ethicon, Inc., et al.</i>	2:12-cv-02952
<i>Sprout, et al. v. Ethicon, Inc., et al.</i>	2:12-cv-07924
<i>Iquinto v. Ethicon, Inc., et al.</i>	2:12-cv-09765
<i>Daniel, et al. v. Ethicon, Inc., et al.</i>	2:13-cv-02565
<i>Dillon, et al. v. Ethicon, Inc., et al.</i>	2:13-cv-02919
<i>Webb, et al. v. Ethicon, Inc., et al.</i>	2:13-cv-04517
<i>Martinez v. Ethicon, Inc., et al.</i>	2:13-cv-04730
<i>McIntyre, et al. v. Ethicon, Inc., et al.</i>	2:13-cv-07283
<i>Oxley v. Ethicon, Inc., et al.</i>	2:13-cv-10150
<i>Atkins, et al. v. Ethicon, Inc., et al.</i>	2:13-cv-11022
<i>Garcia v. Ethicon, Inc., et al.</i>	2:13-cv-14355
<i>Lowe v. Ethicon, Inc., et al.</i>	2:13-cv-14718
<i>Dameron, et al. v. Ethicon, Inc., et al.</i>	2:13-cv-14799
<i>Vanbuskir, et al. v. Ethicon, Inc., et al.</i>	2:13-cv-16183
<i>Mullens, et al. v. Ethicon, Inc., et al.</i>	2:13-cv-16564
<i>Shears, et al. v. Ethicon, Inc., et al.</i>	2:13-cv-17012
<i>Javins, et al. v. Ethicon, Inc., et al.</i>	2:13-cv-18479
<i>Barr, et al. v. Ethicon, Inc., et al.</i>	2:13-cv-22606
<i>Lambert v. Ethicon, Inc., et al.</i>	2:13-cv-24393
<i>Cook v. Ethicon, Inc., et al.</i>	2:13-cv-29260
<i>Stevens v. Ethicon, Inc., et al.</i>	2:13-cv-29918
<i>Harmon v. Ethicon, Inc., et al.</i>	2:13-cv-31818
<i>Snodgrass v. Ethicon, Inc., et al.</i>	2:13-cv-31881
<i>Miller v. Ethicon, Inc., et al.</i>	2:13-cv-32627
<i>Matney, et al. v. Ethicon, Inc., et al.</i>	2:14-cv-09195
<i>Jones, et al. v. Ethicon, Inc., et al.</i>	2:14-cv-09517
<i>Humbert v. Ethicon, Inc., et al.</i>	2:14-cv-10640
<i>Gillum, et al. v. Ethicon, Inc., et al.</i>	2:14-cv-12756
<i>Whisner, et al. v. Ethicon, Inc., et al.</i>	2:14-cv-13023

<i>Tomblin v. Ethicon, Inc., et al.</i>	2:14-cv-14664
<i>Schepleng v. Ethicon, Inc., et al.</i>	2:14-cv-16061
<i>Tyler, et al. v. Ethicon, Inc., et al.</i>	2:14-cv-19110
<i>Kelly, et al. v. Ethicon, Inc., et al.</i>	2:14-cv-22079
<i>Lundell v. Ethicon, Inc., et al.</i>	2:14-cv-24911
<i>Cheshire, et al. v. Ethicon, Inc., et al.</i>	2:14-cv-24999
<i>Burgoyne, et al. v. Ethicon, Inc., et al.</i>	2:14-cv-28620
<i>Bennett, et al. v. Ethicon, Inc., et al.</i>	2:14-cv-29624

## **RULE 26 EXPERT REPORT OF BRUCE ROSENZWEIG, M.D.**

### **I. QUALIFICATIONS.**

I am currently an Assistant Professor of Obstetrics and Gynecology at Rush University Medical Center in Chicago, Illinois. I received my MD degree in 1984 from the University of Michigan in Ann Arbor, Michigan. Following graduation from medical school, I completed an Obstetrics and Gynecology Residency at Michael Reese Hospital in Chicago. In 1988, I attended a one year pelvic surgery fellowship at State University of New York in Syracuse, New York. Following that fellowship, I attended a two year Urogynecology and Urodynamics fellowship at UCLA Harbor General Hospital in Torrance, California. After graduating from the Urogynecology fellowship, I became a faculty member at the University of Illinois in Chicago. I started a Urogynecology program at the University of Illinois and also was the residency program director. In 1998, I went into private practice, and subsequently established a private practice at Rush University Medical Center. I have also worked at John H. Stroger Hospital here in Chicago from May 2003 until November 2010 and Weiss Memorial Hospital as Associate Chair of Gynecology from February 2011 until July 2012. I have published numerous articles and given numerous lectures on the topics of pelvic organ prolapse, urinary incontinence and repair of pelvic organ prolapse.

Throughout my career, I have performed over a thousand pelvic floor surgical procedures, including abdominal sacrocolpopexy, uterosacral suspensions, sacrospinous

ligament fixations, native tissue repairs, biological graft repairs and synthetic mesh repairs. I have also used numerous synthetic pelvic mesh products, including Ethicon's TVT, TVTbutorator, and Prolift. In addition, I have performed over 300 surgeries dealing with complications related to synthetic mesh, including the removal of numerous TVT devices. I have also treated approximately 800 additional patients with mesh non-surgically. I was invited by Ethicon and attended both its Gynecare Prolift Training Seminar and TVT Obturator Seminar in Belgium. In addition, I was invited and attended a Bard Avaulta training seminar in the past.

A copy of my CV and Fee Schedule is attached as Exhibit "A" and a copy of my testimony for the last four years is attached as Exhibit "B". The documents I relied on for this report are contained in Exhibit "C" as well as those documents cited throughout this Report.

## **II. SUMMARY OF OPINIONS.**

In formulating my opinions and preparing this report, I reviewed scientific literature, corporate documents from Ethicon, sample products and depositions of Ethicon employees and witnesses. The corporate documents, sample products and depositions were supplied to me by counsel. A list of Ethicon corporate documents and depositions reviewed for this report is attached hereto as Exhibit "C"; other materials reviewed are listed at the end of this report. All opinions I have are to a reasonable degree of medical and scientific certainty. I understand discovery is still ongoing in this case, and I reserve my right to amend my opinions if further information is provided in any form including, but not limited to corporate documents, depositions and the expert reports of both Plaintiff and Defense experts. My opinions in this Report relate only to the Ethicon Design Consolidation case pending in West Virginia.

In general, my expert opinions can be summarized as follows<sup>1</sup>:

- A. Ethicon's old construction mesh (Prolene), used in the TVT, is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence because the pores are too small, it is heavy weight mesh, it degrades over time, causes chronic foreign body reactions, fibrotic bridging, mesh contracture/shrinkage, fraying, particle loss, biofilm formation and infections, has sharp edges, ropes, curls and deforms, and the pores collapse with tension;
- B. Ethicon knew that the old construction mechanically cut mesh (Prolene) was not appropriate for use in its TVT device but has failed to modify/change the mechanically cut mesh to a larger pore, lighter weight mesh that would not deform, fray, lose particles, rope, curl, degrade, cause excessive foreign body reactions, and cause excessive shrinkage/contraction. According to Ethicon's internal documents, Ethicon was unwilling to change the mesh because of its economic interest in maintaining its competitive advantage in the MUS market and, therefore, Ethicon put profits before patient safety;
- C. Ethicon's TVT's design is flawed because it cannot adequately describe, inform or explain to physicians how to properly "tension" the TVT and the mesh shrinks, contracts, ropes and curls making it difficult or impossible to tension in a safe manner for patients;
- D. Ethicon's Prolene mesh in the TVT is not suitable for permanent implant because the Material Safety Data Sheets ("MSDS") for polypropylene resin used to manufacture polypropylene states that polypropylene is incompatible with strong oxidizers such as peroxides which are readily found in the vagina;
- E. Ethicon's Prolene mesh is also not suitable for permanent implant because the toxicity testing of the polypropylene mesh revealed that it was cytotoxic which can cause cell death and complications;
- F. Ethicon's warnings and disclosures of adverse events in its TVT Instructions for Use ("IFU") have been inadequate based on the adverse reactions and risks associated with the TVT that have been known to Ethicon from the time the TVT was first sold and marketed, and Ethicon did not disclose information to physicians in its IFUs regarding characteristics of the old construction mesh (Prolene) that makes it unsuitable for its intended application as a permanent prosthetic implant for stress urinary incontinence, including that it is small pore, heavy weight mesh, it degrades over time, causes chronic foreign body reactions, fibrotic bridging, mesh contracture/shrinkage, fraying, particle loss, roping and curling of the mesh, that it deforms and the pores collapse with tension, that it is difficult or impossible to tension; that it tested positive for

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<sup>1</sup> This is not intended to be an exhaustive recitation of my opinions in this case. The full scope of my opinions are described in further detail in this report.

cytotoxicity and that the MSDS states that it is incompatible with strong oxidizers such as peroxides.

- G. The design of the TVT device is flawed because it is not designed for special patient populations nor does the IFU or marketing documents inform physicians that certain patients will have poorer outcomes and higher risks.
- H. Ethicon failed to reveal material facts about complication and conflict of interests regarding key studies and in key marketing documents.
- I. The benefits of the TVT are outweighed by the severe, debilitating and life changing complications associated with the TVT and there were safer alternative options available.
- J. It has been known since the launch of the TVT that the mesh can be difficult to remove, is susceptible to degradation, can rope, curl, deform, fray, and lose particles, and is a heavy weight mesh. However, Ethicon did not account for this facts in its dFMEA at the time of launch, and has failed to complete a proper risk analysis of these hazards

### **III. BACKGROUND AND TREATMENT OPTIONS FOR STRESS URINARY INCONTINENCE.**

#### **A. Stress Urinary Incontinence (“SUI”)**

Approximately one of three women over the age of 45 years old has some form of urinary incontinence. The majority of those women do not seek medical advice or treatment for a variety of reasons.

In a continent individual, increased abdominal pressure is evenly distributed over the bladder, bladder neck, and urethra. The urethral sphincter is thus able to withstand this pressure and maintain continence. In a person with pure stress urinary incontinence (SUI), either the urethra is hypermobile or the sphincter is intrinsically deficient. In urethral hypermobility, the urethrovesical junction (UVJ) is displaced extra-abdominally, and the increased intra-abdominal pressure is unevenly distributed such that the sphincter can no longer withstand the pressure and urine leaks. With intrinsic sphincter deficiency (ISD), the UVJ is not hypermobile; however, the maximal urethral closing pressure, the Valsalva leak-

point pressure, or both are too low to withstand the increase in intra-abdominal pressure and, thus, urine leaks past the sphincter.

SUI is the involuntary leakage of urine during moments of physical activity that increases abdominal pressure, such as coughing, sneezing, laughing, or exercise, in the absence of a bladder contraction. It has been estimated that 14% of women have SUI. SUI is a common type of urinary incontinence in women. Urodynamic proven SUI is found in approximately 50% of women presenting for evaluation of urinary incontinence. Symptomatic women with SUI have social or hygienic consequence from their urine loss. SUI can happen when pelvic tissues and muscles, which support the bladder and urethra, become weak and allow the bladder “neck” (where the bladder and urethra intersect) to descend during bursts of physical activity (urethral hypermobility). This descent can prevent the urethra from working properly to control the flow of urine. SUI can also occur when the sphincter muscle that controls the urethra weakens (intrinsic sphincter deficiency). The weakened sphincter muscle is not able to stop the flow of urine under normal circumstances, and when there is an increase in abdominal pressure. Weakness may occur from pregnancy, childbirth, aging, or prior pelvic surgery. It has been estimated that a majority of incontinent women have a combination of urethral hypermobility and ISD. Other risk factors for SUI include chronic coughing or straining, constipation, obesity and smoking. Finally occult or latent SUI is defined as a positive stress test, loss of urine with increased intra-abdominal pressure and between 350-450cc volume in the bladder, after the repositioning of pelvic organ prolapse (usually accomplished with a ring pessary carefully positioned as to avoid compression of the urethra) in an otherwise clinically continent patient.

#### **B. Nonsurgical Treatment of SUI.**

There are numerous non-surgical treatments available to woman with SUI. First,

Pelvic Floor Exercises: A type of exercise to strengthen the pelvic floor by contracting and relaxing the levator muscles that surround the opening of the urethra, vagina, and rectum. These exercises, commonly referred to as Kegel exercises, improve the pelvic floor muscles' strength and function. Kegel exercises can improve over-active bladders by increasing urethral resistance which can trigger the bladder to relax.

Second, Pessary: A removable device that is inserted into the vagina against the vaginal wall and urethra to support the bladder neck. This helps reposition the urethra to reduce SUI. These can be made of rubber, latex or silicon. Inserted into the vagina, a pessary rests against the back of the pubic bone and supports the bladder. Pessaries are available in various forms, including donut and cube shapes, and must be fitted by a healthcare provider. Some women who have stress incontinence use a pessary just during activities that are likely to cause urine leakage, such as jogging. Special incontinence pessaries have a 'knob', which fits under the urethra to elevate the midurethral to prevent urine loss.

Third, Transurethral Bulking Agents: Bulking agent injections are applied around the urethra that makes the space around the urethra thicker, thus helping to control urine leakage. The effects are usually not permanent.

Fourth, Behavioral Modification: This includes avoiding activities that trigger episodes of leaking. Lifestyle modification can improve stress incontinence symptoms and include quitting smoking, weight loss, and allergy treatment during seasonal allergies.

Fifth, Urinary seals: These are adhesive foam pads, which women place over the urethral opening. The pad creates a seal and prevents the leakage of urine, providing incontinence treatment. The pad is removed before urination and replaced with a new one afterward. The pad can be worn during exercise or physical activity, but not during sexual



intercourse.

Sixth, Urethral insert: A thin, flexible tube that is solid rather than hollow (like a catheter) is placed into the urethra to block the leakage of urine. These small plugs are inserted into the urethra by women to prevent leakage, and are removed prior to urination. These inserts can be uncomfortable and may increase the risk of urinary tract infection.

Seventh, Bladder neck support device: This device is a flexible ring with two ridges. Once inserted into the vagina, the ridges press against the vaginal walls and support the urethra. By lifting the bladder neck, it provides better bladder control in women suffering from stress incontinence. The device needs to be sized to fit, and must be removed and cleaned after urination. Bladder neck support devices can be uncomfortable and may cause urinary tract infections.

### **C. Surgical Treatment of SUI.**

#### **1. The Burch Colposuspension.**

Retropubic approaches for the treatment of stress urinary incontinence include the Burch retropubic urethropexy (both open and laparoscopic) and the Marshall-Marchetti-Krantz (MMK) procedure. The goal of both of these procedures is to suspend and stabilize the urethra so that the urethrovesical junction (UVJ) and proximal urethra are replaced intra-abdominally and to recreate a firm backstop for intra-abdominal pressure. This anatomic placement allows normal pressure transmission during periods of increased intra-abdominal pressure restoring continence in a previously incontinent, hypermobile UVJ.

The Burch procedure was described in 1961. Initially, Burch described attaching the paravaginal fascia to the arcus tendineus. However, this was later changed to Cooper's ligaments because these were felt to provide more secure fixation points, and less chance of infection as seen with the prior MMK procedure.

Patients with type III stress urinary incontinence (a fixed, nonfunctioning proximal urethra) are not ideal candidates for a Burch procedure as no hypermobility exists to correct. For the Burch procedure, a low Pfannestiel incision is made above the pubic bone in order to enter the space of Retzius (the anatomical space between the pubic bone and the bladder above the peritoneum in order to suspend the bladder and/or to perform a paravaginal repair. The procedure involves placing permanent stitches adjacent to the neck of the bladder and either proximal or distal to the bladder neck stitches on each side and suturing them Cooper's ligament which is attached to the pubic bone. The paravaginal repair is very similar except that the stitches are attached to the arcus tendentious linea pelvis. The likelihood of success of the Burch and the paravaginal repair procedures is reported to be 80-90% in most cases. Success means total elimination of the incontinence and patient satisfaction score greater than 90%. Improved means significant reduction of urine loss and greater than 70% improvement of patient satisfaction scores. Additionally, these retropubic procedures can be accomplished by the laparoscopic route. With respect to the selection of synthetic absorbable suture versus non-absorbable suture, and braided versus monofilament, no prospective randomized blinded data exist to suggest superiority of one suture material over another. However, recognized risks are associated with bone anchors. Modifications in the technique can be used if co-existent central defect cystocele is present and obliteration of the cul-de-sac can be performed to prevent enterocele or posterior vaginal wall prolapse after Burch colposuspension.

Although the Burch procedure may take longer and require a very small hospitalization, it is a much safer procedure than synthetic slings because life-altering long-term complications do not occur with Burch like they do with synthetic slings, including chronic debilitating pain, chronic sexual dysfunction and dyspareunia, erosions, multiple surgeries to remove mesh,

emotional issues related to sexual dysfunction and many others as discussed throughout this report. Furthermore, if complications do occur following a Burch procedure, they are very rarely long-term and much easier to treat.

## **2. Pubovaginal sling procedures.**

Pubovaginal slings have excelled overall success and durable cure. The procedure involves placing a band of autologous, allograft, xenograft or synthetic material directly under the bladder neck (ie, proximal urethra) or mid-urethra, which acts as a physical support to prevent bladder neck and urethral descent during physical activity. This is brought up through the rectus fascia. The sling also may augment the resting urethral closure pressure with increases in intra-abdominal pressure.

Historically, surgeons have used the fascia lata sling for recurrent SUI after a failed anti- incontinence operation. Furthermore, this operation is used extensively for the treatment of primary ISD. If the abdominal tissues are weak and attenuated or if the vaginal tissues are atrophied or in short supply, constructing a pubovaginal sling from the leg fascia lata can be performed. This procedure is more involved than the creation of the rectus fascial sling as it requires a second incision to harvest the fascia lata and healing in an area remote for the index procedure.

An alternative to a long rectus sling is construction of a short sling from a much smaller piece of abdominal fascia (rectus fascia suburethral sling). The surgical procedure is similar to that used for the rectus fascia pubovaginal sling, except that the harvested fascial tissue is much smaller and the operation time shorter. The advantage of this procedure is its simplicity. No extensive dissection in the suprapubic area is necessary, and the postoperative result is similar to that of the full-length fascial strip sling.

An alternative to a long fascia lata sling is the use of a postage stamp-sized patch of fascia lata from the outer thigh (fascia lata suburethral sling). The surgical procedure is similar to that for the fascia lata pubovaginal sling, except the harvested fascia is much smaller. This operation does not require extensive dissection in the thigh area, and the postoperative result is similar to that of the full-length fascia lata strip sling. Postoperative convalescence is shorter than that of the fascia lata pubovaginal sling procedure.

The vaginal wall suburethral sling helps restore urethral resistance by increasing urethral compression and improving mucosal coaptation of the bladder neck. This operation is attractive because it is simple and easy to perform. Postoperative complications are minimal, and the recuperative period is short. Vaginal sling surgery is relatively contraindicated in elderly women with atrophic vaginitis. If recognized before surgery, the atrophied vaginal wall may be revitalized with the administration of vaginal estrogen cream or tablets for 3-6 months.

A clear contraindication to pubovaginal sling surgery is pure urge incontinence or mixed urinary incontinence (MUI) in which urge is the predominant component. An inherent risk of any sling procedure is de novo or worsening urge symptoms; thus, surgeons must identify and treat the presence of an urge component before surgery.

Conversely, poor detrusor function is a relative contraindication to pubovaginal sling surgery because the potential for urinary retention is increased. Women with absent or poor detrusor function in the presence of SUI are at a higher risk of experiencing prolonged postoperative urinary retention.

### **3. Midurethral Synthetic Slings.**

Based on the “Integral theory of female incontinence,” Prof. Ulmsten developed a midurethral procedure to treat stress urinary incontinence. The first reports of this procedure appeared in 1996 as an intravaginal slingoplasty. The “tape” was placed through a small

vaginal incision at the midurethra, brought through the urogenital diaphragm through the retropubic space and exited through small suprapubic incisions. The operation was theorized to correct incontinence by recreating the midurethral support of the pubourethral ligament and also by creating a midurethral hammock for support of the urethra during stress events. The procedure was described to have a success rate of 85-90% with an additional 5-10% significantly improved. The Gynecare TVT system was introduced in the US in November of 1998. Early studies showed that the risk of bladder perforation during the procedure occurred 5-10% of cases and vascular injury with without hematoma formation occurred in 2-5% of patients.

In an attempt to decrease the risk of bladder perforation and vascular injury, a “top-down” approach to trocar placement was promoted as the SPARC procedure, introduced in the US in 2001 by American Medical Systems (AMS). The next modification of the midurethral sling came in 2001 when Delorme described his results for the use of the obturator membrane and inner thigh for passage of the sling material. The proposed advantage was avoidance of the retropubic space, thus avoiding bladder perforation and retropubic vascular injury. The trocars were passed from the inner thigh through the obturator membrane from an “outside – in direction”.

The next modification came from de Leval in 2003, with the “inside-out” trocar placement for the transobturator sling. This device is the focus of this report. The final modification came around 2006 with the release of the mini-slings, or single incision slings, which use support devices at the ends of shorter mesh lengths to accomplish fixation without the need for a secondary cutaneous exit point. The mini-slings could be placed in a retropubic or “U” fashion or a hammock or “H” fashion.

The FDA concluded in 2011 that there was higher peri-operative blood loss, higher mesh exposure and greater need for surgical re-intervention in the TVT-Secur (mini-sling) patients.

#### IV. EXPERT OPINIONS

- A. Ethicon's old construction mesh (Prolene), used in the TVT, is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence because the pores are too small, it is heavy weight mesh, it degrades over time, causes chronic foreign body reactions, fibrotic bridging, mesh contracture/shrinkage, fraying, particle loss, biofilm formation and infections, sharp edges, roping and curling of the mesh, it deforms, and the pores collapse with tension.**

Polypropylene mesh (Prolene), like that contained in the TVT, has many well-known characteristics that make it unsuitable for use as a product intended for permanent implantation in the human vaginal floor. These characteristics include the following: (1) degradation of the mesh; (2) chronic foreign body reaction; (3) infections and bio-films; (4) fraying, roping, curling and deformation of the mesh; (5) loss of pore size with tension; (6) fibrotic bridging leading to scar plate formation and mesh encapsulation; and (7) shrinkage/contraction of the encapsulated mesh.

As a result of these and other inadequacies with the mesh, and for the reasons set forth below, it is my opinion to a reasonable degree of medical certainty that the Prolene polypropylene mesh in the TVT causes a multitude of injuries, including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, chronic dyspareunia, nerve injury of the pelvic nerves, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, Ethicon's TVT

mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women.

# **1. The Prolene Mesh in TVT Degrades Over Time**

As noted below, the mesh used in the TVT was originally designed in 1974 for use in the abdomen for treatment of hernias and it has not changed since then.<sup>2</sup> Ethicon describes this mesh as the “old, old” mesh: “The first generation (old, old) mesh is utilized currently in the TVT product....”<sup>3</sup> The current Material Specifications for TVT Mesh list it as: “Old Construction PROLENE\* Mesh.”<sup>4</sup> Dan Smith testified that even when the original hernia mesh was updated for use in the abdomen, Ethicon continued to use the “old, old” mesh for TVT and does to this day, as follows:

- Q: So TVT kept the old when hernia changed to the new.  
 A: Also known as original, yes.  
 Q: The mesh that was used in the TVT-R is called sometimes by Ethicon in documents old construction or original mesh; correct?  
 A: Yes. Yes.<sup>5</sup>

In the late 90’s Ethicon determined that, in the hernia applications, it was safer to move to a lighter weight, larger pore mesh. Ethicon made a similar determination for meshes to be used in the pelvic floor.<sup>6</sup> However, Ethicon never updated the “old, old” hernia mesh used in the TVT.<sup>7</sup> Notably, in my opinion this makes science and information regarding hernia meshes and other pelvic meshes of particular relevance when discussing the TVT mesh as Ethicon chose to move to large pore, light weight meshes in these areas, but not for TVT. Moreover, Ethicon relied on science and information regarding hernia meshes to claim the

<sup>2</sup> Smith Dep. (2/3/2014) 723:9-724:6.

<sup>3</sup> Smith Dep. (2/3/2014) 723:9-724:6.

<sup>4</sup> ETH.MESH.10633520 at 3522.

<sup>5</sup> Smith Dep. (2/3/2014) 723:9-724:6.

<sup>6</sup> See, e.g., ETH.MESH.07455220 (discussing mesh shrinkage/contracture and stating: “Since this phenomenon occurs most frequently in small pore, heavy weight mesh, ETHICON has developed large pore, light weight meshes, i.e. GYNECARE GYNEMESH PS Nonabsorbable Prolene Soft Mesh....”).

<sup>7</sup> Smith Dep. (2/3/14) 829:16-829:19.

safety and efficacy of their pelvic mesh products to regulatory bodies.

The placement of permanent polypropylene mesh in the human vagina creates problems because of the chemical composition and structure of the mesh and the physiological conditions of the vagina and the surrounding tissues. There have been numerous studies over the last 30 years which have shown polypropylene to be chemically reactive and not inert, with flaking and fissuring demonstrated by scanning electron microscopy, which leads to degradation and release of toxic compounds into pelvic tissues. This process enhances the inflammatory and fibrotic reactions within the tissues in the pelvic floor, causing a multitude of problems.<sup>8</sup> There have been studies suggesting that oxidation of the mesh occurs because of the polypropylene and the conditions in which it is placed.<sup>9</sup> The oxidation causes the mesh to degrade, crack and break apart.<sup>10</sup> In a recent study, 100 pelvic mesh implants were compared and over 20% showed degradation to mesh fibers.<sup>11</sup>

Because of the structural complexities of the vagina and the nature of the chemicals ordinarily found in the vagina and its surrounding tissues, there are several reasons why polypropylene presents unique problems when placed in the vagina. An Engineering Bulletin from Propex, entitled “*EB-405, The Durability of Polypropylene Geotextiles for Waste Containment Application*,” from 2011, states that, “[P]olypropylene is vulnerable to the following substances: highly oxidized substances such as (peroxide), certain chlorinated

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<sup>8</sup> Coda A., *Hernia* 2003;7:29; Jongebloed, WL, “*Degradation of Polypropylene in the Human Eye: A SEM Study*,” Doc. Ophthalmol., 1986 64(1:143-152); Skrypunch, O.W., “*Giant Papillary Conjunctivitis from an Exposed Prolene Suture*,” Can. J Ophthalmology, 198621:(5: 189-192).

<sup>9</sup> Costello C., et al., “*Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Mesh Explants from a Single Patient*,” Surgical Innovation , 2007, 143:168- 176).

<sup>10</sup> *Id.*

<sup>11</sup> Clavé A, Yahia H, Hammou JC, Montanari S, Gounon P, Clavé H, “*Polypropylene as a Reinforcement in Pelvic Surgery is Not Inert: Comparative Analysis of 100 Explants*,” J Biomed Mater Res B Appl Biomater, 2007, Oct 83(1:44-9).



hydrocarbons (halogenated hydrocarbons), and certain aromatic hydrocarbons.”<sup>12</sup> It is well known to physicians with expertise in the pelvic floor that vaginal and perivaginal tissues are ready sources for peroxide. The vaginal species lactobacillus produces hydrogen peroxide and lactic acid from collagen that is produced in the squamous cells of the vagina. Estrogen is the catalyst for the production of collagen from the vaginal cells. It is also well known that hydrogen peroxide produced by the lactobacillus species is important in controlling the vaginal micro-flora.

In fact, the vagina is a ready source of hydrogen peroxide production. In a manuscript from M. Strus, “*The In Vitro Effects of Hydrogen Peroxide on Vaginal Microbial Communities*,” the authors show the amount of hydrogen peroxide produced by the lactobacillus species.<sup>13</sup> “Hydrogen Peroxide reached concentrations of from 0.05 to 1.0 mm, which under intensive aeration increases even up to 1.8 mm.”<sup>14</sup> These results confirmed the previous results of M. Strus in the publication, “*Hydrogen Peroxide Produced by Lactobacillus Species as a Regulatory Molecule for Vaginal Micro-flora*,” Med Dosw Mikrobiol, 2004: 56(1:67-77).

It is also known that aromatic hydrocarbons can be found in the human body. In a paper from HB Moon entitled, “*Occurrence and Accumulation Patterns of Polycyclic Aromatic Hydrocarbons and Synthetic Musk Compounds in Adipose Tissues of Korean Females*,” Chemosphere 2012 (86:485-490), these aromatic hydrocarbons were noted to be present in, “[t]otal concentrations of PAHs and SMCs in adipose tissues rang[ing] from 15 to 361 (mean:119) ngg(-1) lipid weight and from 38 to 253 (mean:106) nng(-1)

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<sup>12</sup> Citing Schneider H., *Long Term Performance of Polypropylene Geosynthetics*, “*Durability and Aging of Geosynthetics*, Koerner, RM, Ed., (Elsevier 1989) 95-109.

<sup>13</sup> Strus, M., et al., *The In Vitro Effect of Hydrgen Peroxide in Vaginal Microbial Communities*, FEMS Immunol Med Microbiol, 2006 Oct; 48(1:56-63).

lipid weight respectively.... The results of this study provide baseline information on exposure of PAHs and SMCs to the general population in Koreans."

It has also been determined that halogenated hydrocarbons can be found not only in adipose tissue but also the blood stream. A paper entitled, "*Determination of Volatile Purgeable Halogenated Hydrocarbon in Human Adipose Tissue and Blood Stream*," from the *Bulletin of Environmental Contamination and Toxicology*, Volume 23, Issue 1, pp 244 – 249 published in 1979, found halogenated hydrocarbons, pesticide by-products, both in human adipose tissues and the blood stream. In a subsequent paper from 1985 in *Environmental Health Perspectives*, Volume 60, pp. 127-131, Henry Anderson, in his paper entitled, "*Utilization of Adipose Tissue Biopsy and Characterizing Human Halogenated Hydrocarbon Exposure*," also found these pesticide by-products in human adipose tissue. Accordingly, the body location where the polypropylene mesh is being placed can expose it to known chemical degradation agents.

However, chemical degradation is not the only way that polypropylene degrades *in vivo*. In a paper from N Das in the Journal of Biotechnology Research International, Volume 2011, Article ID 941810, entitled, "*Review Article: Microbial Degradation of Petroleum Hydrocarbons Contaminant: An Overview*," found that various bacteria such as Pseudomonas species, Bacillus species, Mycobacterium and Corynebacterium species, which are present in a woman's vagina, can degrade petroleum hydrocarbons. Also fungi such as the Candida species, also present, can degrade petroleum-based hydrocarbons.<sup>15</sup> Microbial agents that can be found inside the normal and abnormal flora of the human vagina such as Candida and, with

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<sup>14</sup> *Id.*

<sup>15</sup> Das, N., et al., *Review Article: Microbial Degradation of Petroleum Hydrocarbon Contaminants: an Overview*, J Biotech Res Intl, 2011, Article ID 941810, 1-13.

certain pelvic infections such as *Bacillus* and *Pseudomonas*, can be a source of biological degradation of polypropylene products.

A paper entitled, “*Health, Safety and Environment Fact Sheet: Hazardous Substances - Plastics*,” from CAW/TCA ([www.caw.ca](http://www.caw.ca)), August 2011:343, found that polypropylene degradation products and residues can form carbon monoxide, acrolein, aldehydes and acids, qualifying these health hazards as toxic and irritants. In a paper from D Lithner in 2011 at 4, entitled, “*Environmental and Health Hazards of Chemicals in Plastic Polymers and Products*,” University of Gothenburg, it is stated that, “[n]on-biodegradable polymers can be degraded by heat, oxidation, light, ionic radiation, hydrolysis and mechanical shear, and by pollutants such as carbon monoxide, sulphur dioxide, nitrogen oxide and ozone. This causes the polymer to get brittle, to fragment into small pieces and to release degradation products.” (Citations omitted.) Lithner continues, “[o]ther substances (besides monomers) are often needed for polymerization to occur, for instance initiators, catalysts, and, depending on manufacturing process, solvents may also be used. The resulting plastic polymer can be blended with different additives, for instance plasticizers, flame retardants, heat stabilizers, antioxidants, light stabilizers, lubricants, acid scavengers, antimicrobial agents, anti-static agents, pigments, blowing agents and fillers, and is finally processed into a plastic product. There are many different plastic polymers and several thousand different additives, which result in an extremely large variation in chemical composition of plastic products.” *Id.* at 6 (citations omitted). “Since plastic products are composed of many different chemicals, and the main part of these [are] broken down into something completely different; this complicates the prediction.” *Id.* at 8. “The type and quantity of degradation products formed may also be influenced by degradation mechanisms, presence of polymerization impurities, and surrounding factors, e.g. temperature and oxygen.”

*Id.* at 9. “Few studies combining leaching tests with toxicity tests have been performed on plastic products.” *Id.* at 12. The available peer-reviewed literature regarding degradation/oxidation of polypropylene in the human body dates back to the 1960’s and has been reported in numerous such publications.<sup>16</sup>

Two of the more important and salient articles regarding reported degradation in explanted surgical meshes (hernia and pelvic floor) are the Costello and Clave articles. In his paper, “*Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Implants from a Single Patient*,” Prof. C Costello reported that hernia mesh made of polypropylene oxidized and degraded as a result of the metabolites produced by phagocytic cells during the body’s inflammatory reaction to the mesh. High-magnification photographs showed cracking and peeling of the polypropylene fibers. Ethicon referenced this article in internal emails.<sup>17</sup>

Another article by A Clave, “*Polypropylene as a Reinforcement in Pelvic Surgery is Not Inert: Comparative Analysis of 100 Explants*,” also displayed high magnification photos of polypropylene fibers from explanted meshes and, in this case, the meshes were explanted from women’s pelvic floor tissue.<sup>18</sup> The heavyweight meshes showed even greater cracking than the lower density meshes, but according to Prof/Dr. Clave, ALL 84 of the polypropylene explants examined showed degradation. Oxidation of the implanted mesh due to free radical attack through the synthesis of peroxides, superoxides and hypochlorous acid during the chronic inflammatory phase was listed as just one potential cause for the oxidative degradation

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<sup>16</sup> Liebert, T, et al., *Subcutaneous Implants of Polypropylene Filaments*, J Biomed Mater Res. 1976 (10:939-951); Williams, D., *Review of Biodegradation of Surgical Polymers*, J Materials Sci, 1982 (17:1233-1246); Oswald, H.J., et al., *The Deterioration of Polypropylene By Oxidative Degradation*, Polymer Eng Sci, 1965 (5:152-158).

<sup>17</sup> ETH.MESH.005588123.

<sup>18</sup> Clave, A., *Polypropylene as a Reinforcement in Pelvic Surgery is Not Inert: Comparative Analysis of 100 Explants*, I Urogynecol J 2010 21:261-270.

within the “septic environment” in which the pelvic meshes are placed.

Given the information available to Ethicon in the scientific and medical literature concerning the potential for degradation of polypropylene, it is my opinion to a reasonable degree of medical certainty that Ethicon should have conducted clinically relevant testing to determine if naturally occurring conditions in the vagina could cause polypropylene to degrade and if so, what the quantity and quality of the products of degradation would be, whether they would be released into surrounding tissues and/or migrate in the woman’s body, what the clinical implications for the woman would be and whether some women’s bodies would react differently to the mesh and degradative process and its by-products.

Ethicon’s Daniel Burkley, a Principal Scientist at Ethicon, testified that the science supported the conclusion that mesh could shrink, contract and degrade. Specifically, Mr. Burkley agreed that the risk of degradation increases when you have a severe inflammatory response with mesh implanted in a contaminated field.<sup>19</sup> Mr. Burkley also testified that polypropylene mesh in human beings is subject to some slight degree of surface degradation.<sup>20</sup> He agreed that degradation might be better understood if Ethicon studied or tested a product that is permanently implanted in women.<sup>21</sup> In fact, according to Mr. Burkley, Ethicon only conducted one study related to degradation and Prolene material. This study consisted of a Prolene suture implanted into dogs.<sup>22</sup> Mr. Burkley testified that the study and photos from the dog actually showed that the Prolene material used in TVT degraded and was still degrading after 7 years.<sup>23</sup>

It is now clear from Ethicon’s internal documents that Mr. Burkley was incorrect when

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<sup>19</sup> Burkley Dep. (5/22/13) 184:17-24.

<sup>20</sup> Burkley Dep. (5/22/13) 206:2-11

<sup>21</sup> Burkley Dep. (5/22/13) 206:12-25.

<sup>22</sup> ETH.MESH.05453719 (Seven year data for ten year Prolene study: ERF 85-219).

he said that Ethicon only performed one study related to degradation of Prolene. Contrary to Mr. Burkley's claim, he and other Ethicon scientists were involved in a Prolene human explant study that was conducted in 1987 which found that Prolene degrades while in the body. According to Ethicon's documents, Ethicon's scientists received 58 Prolene human explants from Professor Robert Guidon<sup>24</sup> which were analyzed by Ethicon's scientists using scanning electron microscopy ("SEM"). The SEM study revealed that 34 of the 58 Prolene explants (58%) were cracked. Further studies, including FTIR and melt point analysis, were conducted by Ethicon's scientists to determine the cause of the cracking observed in Prof. Guidon's explants. In a report authored by Mr. Burkley on September 30, 1987, he concluded that the Prolene explants had insufficient antioxidants to protect them from oxidation which led to *in vivo* degradation of the Prolene devices.<sup>25</sup> Importantly, Ethicon has not made any changes to Prolene since it was introduced to the market, except that, in 2011, they reduced the amount of Sanatanox (another antioxidant), which could potentially make Prolene more, not less, susceptible to oxidized degradation.<sup>26</sup> Thus, Ethicon's internal studies clearly demonstrate that Ethicon's scientists had concluded that Prolene can degrade while implanted in the human body.

Ethicon subsequently hired an outside consulting firm to resolve the cause of the erosion of its surgical meshes for the pelvic floor. In a June 22, 2011 report, PA Consulting Group informed Ethicon that, "[p]olypropylene can suffer from degradation following implant... a process which initiates after a few days post implantation in animal studies."<sup>27</sup>

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<sup>23</sup> Burkley Dep. (5/23/13) 315:8-13.

<sup>24</sup> DEPO.ETH.MESH.00004755

<sup>25</sup> ETH.MESH.12831391 at ETH.MESH.1281392

<sup>26</sup> ETH.MESH.02589032 and ETH.MESH.07192929 (May 18, 2011 PA Consulting Report: Investigating Mesh Erosion in Pelvic Floor Repair and PowerPoint presentations

<sup>27</sup> ETH.MESH.02589032 and ETH.MESH.07192929 (May 18, 2011 PA Consulting Report: Investigating Mesh Erosion in Pelvic Floor Repair and PowerPoint presentation).

The consulting report discusses numerous images of polypropylene mesh that show “physical degradation” of the mesh.<sup>28</sup> In addition, in a 2009 presentation, Ethicon Medical Director Piet Hinoul stated that meshes are not biologically inert.<sup>29</sup>

I have personally seen mesh that is broken, cracked, brittle and look different from when it came out of the package. Interestingly, despite years of scientific literature, its own internal dog study, performed by consultants it hired, showing that degradation of mesh occurs, and even despite the fact that Ethicon’s own internal risk assessments include degradation as a known risk, Ethicon’s Instructions for Use (IFU) continues to claim to this day that the mesh in the TVT “is not absorbed, nor is it subject to degradation or weakening by the action of enzymes.”<sup>30</sup> This is not simply inaccurate, but is false and misleading for all of the reasons stated above, including, most importantly, that Ethicon’s own internal documents and testimony from its employees confirm that the mesh degrades.

It is my opinion to a reasonable degree of medical certainty that the mesh used in TVT degrades. The effect of chemical and biological degradation of the TVT Prolene mesh in a woman’s tissues can lead to a greater foreign body reaction, enhanced inflammatory response and excessive scarring, which can lead to severe complications in patients, including the possibility of multiple erosions that can occur throughout one’s lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries,

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<sup>28</sup> *Id.*

<sup>29</sup> ETH.MESH.01264260 (Presentation, “Prolift+M,” P Hinoul, MD, Ethicon Pelvic Floor Expert’s Meeting – Nederland, Utrecht, May 7, 2009).

<sup>30</sup> May 2015 TVT IFU; ETH.MESH.02340406

among others. As a result, the polypropylene in Ethicon's TVT mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women.

Given the information available in the scientific and medical literature concerning the potential for degradation of polypropylene, it is my opinion to a reasonable degree of medical certainty that Ethicon should have conducted clinically relevant testing to determine if naturally occurring conditions in the vagina could cause polypropylene to degrade and if so, what the quantity and quality of the products of degradation would be, whether they would be released into surrounding tissues and/or migrate in the woman's body, what the clinical implications for the woman would be and whether some women's body's would react differently to the mesh and the degradative process and its by-products.

Moreover, Ethicon failed to inform physicians or patients about the potential for degradation of the mesh and the complications that could follow. In fact, Ethicon not only failed to disclose these risks to physicians and patients, it did not accurately describe these significant risks by calling them "transitory" and by putting inaccurate statements about degradation in its IFU. This is information physicians need to know in order to have a fair and proper conversation with their patients about the use of a product. Physicians rely on device manufacturers to inform them of the risks and complications associated with their products instead of downplaying them or inaccurately stating them. By not disclosing this safety information to physicians and their patients, it is my opinion to a reasonable degree of medical certainty that Ethicon failed to properly inform physicians and patients about the risks of degradation of Prolene mesh in the TVT. In addition, by failing to inform physicians, Ethicon did not provide them with an opportunity to adequately discuss these risks with their



patients.

## 2. Chronic Foreign Body Reaction

The human body has a natural and fairly predictable “host defense response” to any foreign object placed inside of it. Whether a splinter or a surgical mesh, the human body will send white blood cells to attack the invader and, if the products of inflammation cannot ward off or destroy the invader, including if the invader is anything from bacteria to prosthetic implants, the initial acute inflammatory phase is followed by a chronic inflammatory phase. Therefore, with the placement of something like a permanent surgical mesh in human tissues, there will be a chronic or permanent foreign body reaction to the implant, as well as a chronic inflammatory response by the body.<sup>31</sup> In fact, Ethicon Medical Directors, Piet Hinoul and Charlotte Owens, have both testified that the chronic foreign body reaction created by the body’s response to mesh can cause a severe inflammatory reaction, which can cause chronic pain, nerve entrapment, erosions, dyspareunia and the need for additional surgeries.<sup>32</sup>

Consultants and experts in the field informed Ethicon that there would be chronic tissue reaction to its polypropylene meshes. During a 2006 meeting at one of Ethicon’s facilities, Bernd Klosterhalfen, a pathology consultant expert for Ethicon, informed Ethicon that there can be a continuing reaction between tissues in the body and mesh for up to 20 years.<sup>33</sup> In addition, during a February 2007 meeting, Ethicon stated that there can be, “[E]xcessive FBR [foreign body reaction]> massive scar plate > more shrinkage.”<sup>34</sup>

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<sup>31</sup> Klinge, U., et al., *Shrinking of Polypropylene Mesh In Vivo: An Experimental Study in Dogs*, Eur J Surg 1998, 164: 965-969; Klinge, U., *Foreign Body reaction to Meshes Used for the Repair of Abdominal Wall Hernias*, Eur J Surg 1998, 164:951-960; Klosterhalfen, B., *The lightweight and large porous mesh concept for hernia repair*, Expert Rev. Med. Devices 2005, 2(1); Binnebosel M, et al., *Biocompatibility of prosthetic meshes in abdominal surgery*, Semin Immunopathol 2011, 33:235-243; ETH.MESH.03658577 (Biocompatibility of Ultrapro).

<sup>32</sup> Hinoul Dep. (4/5/12) 99:09-25; (4/6/12) 518:14-520:20; (6/26/13) 175:1-176:17; 184:18-22; 328:10-24; Owens Dep. (9/12/2012) 98:11-99:07.

<sup>33</sup> ETH.MESH.00870466 (June 6, 2006 Ethicon Expert Meeting Meshes for Pelvic Floor Repair, Norderstedt).

<sup>34</sup> ETH.MESH.01218361 (Ethicon Presentation: “State of Knowledge in ‘mesh shrinkage’-What do we know”).

Internally, Ethicon's scientists agreed. Dr. Holste testified that chronic foreign body reactions occurs in Ethicon's small pore, heavyweight meshes like the Prolene mesh found in TVT.<sup>35</sup> In fact, Dr. Holste testified that Ethicon developed lighter weight, large pore meshes in order to minimize the complications seen with heavyweight meshes like the Prolene used in TVT.<sup>36</sup> Ethicon employee, Christophe Vailhe, testified that there can be an excessive inflammatory reaction or foreign body reaction that would lead to mesh erosion and contraction.<sup>37</sup> Despite its knowledge about the problems associated with chronic foreign body reaction, Ethicon continues to use a heavyweight, small pore mesh in its TVT product.

Contrary to this scientific evidence, Ethicon informed doctors in its IFU that its TVT mesh was "non-reactive with a minimal and transient foreign body reaction," until the IFU was updated in 2010 to remove the word "transient."<sup>38</sup> This was despite all of the internal documents and testimony discussed above from Ethicon's Medical Affairs and Research and Development employees that chronic foreign body reaction occurs in small pore, heavyweight meshes like the Prolene mesh in TVT. Moreover, as one of Ethicon's lead engineers stated: "the foreign body reaction is not transitory – it doesn't ever go away, but decreases over time to a minimal level."<sup>39</sup> That is, it is chronic. I have reviewed numerous pathology reports from my own patients and other physician's patients and pathology reports reviewed in litigations describing foreign body reactions. Hence, the mesh potentiates a chronic, long-term inflammation. This is contrary to the express language of the TVT IFU up until 2010 and, to this date, the IFU still does not state the foreign body reaction is chronic.

Even before Ethicon launched the TVT with the heavyweight, old construction mesh

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<sup>35</sup> Holste Dep. (7/29/13) 52:5-55:21.

<sup>36</sup> Holste Dep. (7/29/13) 51:3-53:6.

<sup>37</sup> Vailhe Dep. (6/21/13) 383:8-19.

<sup>38</sup> ETH.MESH.02340406; ETH.MESH.02340531; TVT IFU, May 2015

for sale in the United States. Ethicon knew that Prolene mesh was far from being the ideal material for use in vaginal tissues.<sup>40</sup> However, despite knowing this, Ethicon decided to launch the product for use in repair of anterior prolapse, in order to gain entry into the market before competitors. Ethicon also knew that doctors had expressed fears about rejection and problems with removing the mesh at a later date, fear of infection, concern that the mesh could erode into the bladder or rectum, and concern about the stiffness of the mesh and the risk of the mesh protruding through the vagina. Even knowing of these concerns regarding the use of Prolene mesh in women's vaginal tissues, Ethicon proceeded to launch the TVT with the heavyweight, 1974 old construction Prolene mesh.

For the reasons set forth above, it is my opinion to a reasonable degree of medical certainty that the Prolene polypropylene mesh in the TVT creates a chronic foreign body reaction which can lead to severe complications in patients, including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, the polypropylene in Ethicon's TVT mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women.

Moreover, Ethicon failed to inform physicians or patients about the potential for a severe, chronic foreign body response and the complications that could follow. In fact, not only did Ethicon fail to disclose these risks, it mischaracterized the risks by calling them

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<sup>39</sup> ETH.MESH.00211259.

<sup>40</sup> ETH.MESH.12009027

“transitory” and by putting inaccurate statements about foreign body response in its IFU. This is information physicians need to know in order to have a fair and proper conversation with their patients about the use of a product. Physicians rely on device manufacturers to inform them of the risks and complications associated with its products instead of downplaying them or inaccurately stating them. By not disclosing this safety information to physicians and their patients, it is my opinion to a reasonable degree of medical certainty that Ethicon failed to properly inform physicians and patients about the risks of foreign body response of Prolene mesh in the TVT. In addition, by failing to inform physicians, Ethicon did not provide them with an opportunity to adequately discuss these risks with their patients.

### 3. Infections/Bio-films

The placement of midurethral slings, including TVT, violates one of the most basic tenets of surgical teachings in that it is the placement of a permanent implant into the patient through a “clean contaminated” surgical field, *i.e.* the vagina, which is not sterile and can never be completely sterilized.

In TVT, the weave of the mesh produces very small interstices which allow bacteria to enter and to hide from the host defenses designed to eliminate them. The bacteria can secrete an encasing polysaccharide slime (biofilm), which further serves to shield the bacteria from destruction by white blood cells and macrophages.<sup>41</sup> The effect and consequences of biofilm is to increase the foreign body reaction, resulting in chronic infections, chronic inflammation, erosions, and mesh and scar contracture, and was well known to Ethicon, as

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<sup>41</sup> Osterberg, B., et al., *Effect of Suture Materials on Bacterial Survival in Infected Wounds: An Experimental Study*, Acta. Chir. Scand 1979, 145:7 431-434; Merritt, K., *Factors Influencing Bacterial Adherence to Biomaterials*, J Biomat Appl 1991, 5:185-203; An, Y., *Concise Review of Mechanisms of Bacterial Adhesion to Biomaterial Surfaces*, J Biomed Mater Res (Appl Biomat) 1998, 43:338-348; The TVM Group: J. Berrocal, et al., *Conceptual advances in the surgical management of genital prolapsed*, J Gynecol Obstet Biol Reprod 2004, 33:577-587.

evidenced by the testimony of Ethicon's Head of Pre-Clinical, Dr. Joerg Holste.<sup>42</sup>

Importantly, the biofilm actually serves as a protection for the bacteria surrounding the mesh fibers against the body's host defense response (white blood cells), which are intended to destroy foreign invaders like bacteria. Thus, the weave induces the creation of a shield against the body's defenses to the bacteria entrained in the woven mesh, inhibiting the body's ability to fight off the infective agents within the mesh. The large surface area promotes wicking of fluids and bacteria which provides a safe haven for bacteria which attach themselves to the mesh during the insertion process.<sup>43</sup> Daniel Burkley testified that reducing surface area could reduce the amount of chronic inflammation.<sup>44</sup> Additionally, the size of the mesh placed equates to a large surface area with many places for bacteria to hide while being protected from host defenses leading to numerous complications.<sup>45</sup>

There have been numerous peer-reviewed journal articles regarding secondary-mesh related infections as well as the dangers of implanting surgical mesh in a clean/contaminated field. Of note, in May of 2013, at the AUA meeting in San Diego, Dr. Shah and his colleagues reported on the "*Bacteriological Analysis of Explanted Transvaginal Meshes*," which included explanted samples of both SUI slings and prolapse meshes. Of the 50 explants examined, 52% of those explanted due to patient complaints' of painful mesh were infused with pathogenic organisms, 20% of those explanted due to vaginal erosions had pathogenic organism, and 83% of those explanted due to urinary tract erosions

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<sup>42</sup> Holste Dep. (7/30/13) 295:24-298:14, 411:15-414:24.

<sup>43</sup> Klinge, U., et al., *Do Multifilament Alloplastic Meshes Increase the Infection Rate? Analysis of the Polymeric Surface, the Bacteria Adherence, and the In Vivo Consequences in a Rat Model*, J Biomed Mater Res 2002, 63:765-771; Vollebregt, A, et al., *Bacterial Colonisation of Collagen-Coated Polypropylene Vaginal Mesh: Are Additional Intraoperative Sterility Procedures Useful?*, Int Urogyn J 2009, 20:1345-51.

<sup>44</sup> Burkley Dep. (5/22/13) 371.

<sup>45</sup> Klinge, *supra* n. 26; Vollebregt, *supra* n. 26.

were contaminated with pathogenic organisms.<sup>46</sup>

When polypropylene particles separate from the surface of the mesh fiber due to degradation, see *infra*, the surface area of the mesh is greatly increased thus providing even greater areas for bacterial adherence to the mesh, more elution of toxic compounds from the polypropylene, and also more of the free toxic polypropylene itself, all of which increases the inflammatory reaction and intensity of the fibrosis.<sup>47</sup> This cracking of the mesh surface also provides safe harbors for infectious bacteria to proliferate.

In his periodic histopathological analyses for Ethicon of its pelvic floor explants, Dr. Klosterhalfen reported to Ethicon that, in virtually 100% of those instances in which mesh had been explanted due to erosions, he found a secondary, mesh-related infection at the tissue/mesh interface.<sup>48</sup> Mesh exposure and erosion cause the fibers to be further exposed to bacteria that will adhere to and colonize on the mesh surface.

Ethicon employees have testified that they were aware of these biofilms forming on the surface of the mesh.<sup>49</sup> However, Ethicon never performed any long-term, clinical studies to determine whether the warnings given them through the peer-reviewed literature and by their own experts and consultants were accurate, namely that mesh-related infections are real; that they cause patient injury in the form mesh erosions and recurrent, late infections; and that the transvaginal implantation through and into the non-sterile, septic vagina is below the standard of care for any surgical technique, especially one used to treat non-life threatening conditions, such as stress urinary incontinence.

Therefore, it is my opinion to a reasonable degree of medical certainty that the TVT

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<sup>46</sup> Shah, K., et al., Bacteriological Analysis of Explanted Transvaginal Meshes (Abstract 1144).

<sup>47</sup> Jongebloed, *supra*, n. 1; Sternschuss, G, et al., *Post-Implantation Alterations of Polypropylene in the Human*, J Urol 2012, 188:27-32; Clave, *supra*, at 6.

<sup>48</sup> ETH.MESH. 00006636.

mesh is susceptible to biofilm formation due to the weave of the mesh allowing the infiltration, harboring, and protection of bacterial contaminants; the degraded mesh surface harboring bacteria; the passage through and into a clean/contaminated field; and after exposure/erosion of the mesh into the vagina or other organs, further contamination of the mesh with a multitude of vaginal flora that further increases the risk of harmful and recurrent infections in women. Accordingly, the TVT transvaginal technique, as well as the TVT mesh itself, are not safe for their intended purpose of implantation into a woman's pelvic tissues and can lead to severe complications in patients, including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, the polypropylene in Ethicon's TVT mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women.

Finally, Ethicon's claims in its IFU that the TVT mesh may "potentiate infection" are misleading, at best. If, by the intentionally ambiguous term, "potentiate," Ethicon means "cause," then this is true for all of the reasons stated above. If by "potentiate," Ethicon means "exacerbate an existing infection," then the statement is misleading at best. Ethicon failed to warn physicians and patients that a slimy, protective biofilm could form on the mesh leading to painful erosions, recurrent, late infections and the need for mesh removal. The TVT IFU contrasts sharply with the PROLENE IFU on this issue. The PROLENE IFU states as follows: PROLENE Mesh in contaminated wounds should be used with the understanding that

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<sup>49</sup> Holste Dep. (7/30/13) 283:19-284:5.

subsequent infection may require removal of the material.<sup>50</sup>

Ethicon did not to include this risk, despite that unlike hernia mesh, TVT mesh is being implanted through a contaminated environment – the vagina. By failing to include this risk, Ethicon did not adequately warn physicians about these important risks, nor by extension, provide surgeons with an opportunity to discuss these risks with their patients.

#### **4. Pore Size and Fibrotic Bridging**

Fibrotic bridging occurs when the fibers surrounding the pores of the mesh are too close together to allow the tissue in the pore enough room to recover from the trauma of tissue damage due to implanting a surgical prosthetic device. Pores that are large enough for good, newly-vascularized tissue tend to be filled with fatty tissue versus small pores that become filled with scarred or fibrotic tissue. In those instances, the scar forms across the pores or “bridges” from one side of the pore to the other. This can occur either due to the granulomas around the mesh fibers joining together or due to densely-formed fibroblasts between these granulomas. Either way, such bridging can lead to the creation of a rigid, scar plate that can encapsulate the mesh with scar tissue. Simply put, small mesh pores that cause fibrotic bridging turn the mesh into a solid sheet of scar tissue and there is no space or room for tissue to grow into the mesh, which is the intended purpose of the mesh. The fibrotic bridging and scar plate prevents tissue in-growth and causes complications, including, among other things, pain with the rigid mesh, shrinkage or contraction of the mesh, erosions due to mechanical irritation in the tissue of a rigid, scar-plated mesh, nerve entrapment, chronic pain and dyspareunia.

This concept is best illustrated by a DVD produced by Ethicon which features an

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<sup>50</sup> ETH.MESH.02342102.



Ethicon consultant, Dr. Todd Heniford, talking about a heavyweight, small pore mesh called Marlex used for hernia repairs.<sup>51</sup> The Prolene mesh used in TVT is of heavyweight, small pore construction and, in fact, is even heavier than Marlex. Ethicon Scientists have acknowledged that the Marlex mesh in the video is similar to the Prolene in TVT in that is heavy weight small pore mesh.<sup>52</sup> Ethicon has also relied on the works of Dr. Heniford relating to lightweight mesh and cited to his works in their marketing materials and professional educational materials for pelvic mesh products. Moreover, Ethicon relied on science and information regarding hernia meshes to claim the safety and efficacy of their pelvic mesh products to regulatory bodies. At least one medical director at Ethicon, Dr. Thomas Divilio, has described the work done by Dr. Heniford and others as “material science” that would apply to both hernia and pelvic mesh products. In my opinion this the video, as well as other science and information regarding hernia meshes and other pelvic meshes of particular relevance when discussing the TVT mesh as Ethicon chose to move to large pore, light weight meshes in these areas, but not for TVT.

In the video, Dr. Heniford talks about the dangers of heavy weight, small pore meshes.<sup>53</sup> In fact, Dr. Heniford states, “there is no excuse for using heavy weight, small pore meshes in the human body.”<sup>54</sup> I have explanted numerous TVT and TVT meshes and have witnessed meshes with extensive scar plating and mesh encapsulation similar to the hardened/stiffened mesh viewed in the Heniford video. In numerous emails, Ethicon employees

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<sup>51</sup> Heniford, B.T., 2007, *The benefits of lightweight meshes in Ventral Hernia Repair in Ventral Hernia Repair*, Video produced by Ethicon.

<sup>52</sup> ETH.MESH.05918776 (5/04/04 Email from Schiaparelli, Jill, Strategic Grown Subject: Marlex Experience); Batke Dep. (8/01/13) 87:12 - 88:10, 113:3-114:3, 257:23-259:13; Holste Dep (7/29/13) 51:3-53:6, 55:22-57:4; Vailhe Dep. (6/20/13) 182:2 185:5.

<sup>53</sup> Heniford Video, supra, n. 46.

<sup>54</sup> *Id.*

discussed concerns regarding fibrotic bridging.<sup>55</sup> They have testified that the heavy weight, small pore type of mesh in the TVT can lead to an increased risk of foreign body reaction, contraction of the mesh, nerve entrapment, erosions and chronic pelvic pain.<sup>56</sup>

In other emails, when discussing these concepts, Ethicon's World Wide Marketing Director for General Surgery, Marty Chomiak, states that "... we want to avoid 'bridging', therefore we think large pores are better than small . . .".<sup>57</sup> Ethicon also had information and scientific knowledge regarding superior mesh designs to prevent fibrotic bridging and scar plating. Specifically, Ethicon also had scientific knowledge that light weight, large pore mesh could decrease the likelihood of foreign body reaction, fibrotic bridging and scar plating.<sup>58</sup>

Despite having clinical knowledge of the importance of pore size to successful outcomes, and dozens of emails about the importance of pore size, Ethicon's person most knowledgeable about pore size testified that Ethicon does not manufacture its mesh to a specific pore size. Dan Smith testified as follows:

- Q: Does Ethicon have a validated test method to determine the pore size of its TVT mesh?
- A: We determine the pore size by courses and wales and that is how it's done. So the courses and wale count is a validated test method.
- Q: And I'm talking about pore size. Does Ethicon have a validated test method to determine its pore size for its mesh?
- A: The construction of the mesh is -- does not have a pore size requirement.<sup>59</sup>

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<sup>55</sup> ETH.MESH.04037600 (Innovations in mesh development); ETH.MESH.05920616 (7/20/07 ; Emails from Chomiak, M. to Batke, B., et al. re Defining light weight mesh); ETH.MESH.05585033 (Boris Batke Presentation – Project Edelweis – Ultrapro); ETH.MESH.05446127 (3/13/2006 Emails from Holste, J. to Engel, D., et al. re Mesh and Tissue Contraction in Animal – “Shrinking Meshes?”); ETH.MESH.05475773 (2/09/2007 Boris Batke, Ethicon R&D, Presentation: *The (clinical) argument of lightweight mesh in abdominal surgery*); ETH.MESH.04015102 (3/1/12 Email from Batke, Boris to Mayes, C. re AGES Pelvic Floor Conference-Gala Dinner Invitation); ETH.MESH.04037600 (3/15/12 Boris, B. PowerPoint Presentation, *Innovations in Mesh Development*, Melbourne AGES 2012).

<sup>56</sup> Batke Dep. (8/1/13) 87:12-88:10, 113:3-114:3, 257:23-259:13; Holste Dep. (7/29/13) 51:3-53:6, 55:22-57:4; Vailhe Dep. (6/20/13) 182:2-185:5.

<sup>57</sup> ETH.MESH.05920616 (7/20/07 Email from Chomiak, M. re Defining Light Weight Mesh).

<sup>58</sup> Batke Dep. (8/1/13) 87:12-88:10, 113:3-114:3, 257:23-259:13; Holste (7/29/13) 51:3 - 53:6, 55:22 - 57:4; Vailhe Dep. (6/20/13) 182:2-185:5.

<sup>59</sup> Smith Dep. (2-3-14) 729:1 to 729:12.

In fact, Ethicon does not even have a test to measure the pore size of its mesh. Dan Smith testified:

- Q. Mr. Smith, does Ethicon have a validated test to describe the pore size of its TVT meshes microns? Yes or no.  
 A. No....<sup>60</sup>

Despite this information that it did not measure pore size or manufacture its mesh to a specific requirement, Ethicon repeatedly stated in advertising and marketing materials that its mesh was “large pore.” For example, in one brochure, Ethicon promotes the mesh used in the TVT family of products (including TVT) as the “Largest pore size” of any of its competitors, listing the size as 1379 um.<sup>61</sup> However, given that Ethicon has no verified methodology to measure pore size, Ethicon had no scientific basis upon which to base these statements. In fact, in internal documents, Ethicon scientists described PROLENE mesh as small pore: “Standard Mesh PROLENE small pores area weight 105 g/m2.”<sup>62</sup> One Ethicon Engineer measured a mesh and determined that there were two pore sizes in the mesh, a “major” and “minor” pore. “There are two distinct pore sizes in the PROLENE 6 mil mesh (TVT). The major pore is about 1176 um.... The minor pore is about 295 um.”<sup>63</sup> Certainly, neither of these pores was 1379 um, and the minor pore was substantially smaller.

In addition, the pore size of a mesh can change when the mesh is put under stress such as when a sheath is removed or the mesh is tensioned. Dan Smith agreed that these stresses can make an effective pore size smaller than 1 mm.

- Q. You would agree, Mr. Smith, that if the measurement across the pores we're looking at here -- let's assume you measure across one of those pores and let's say it's more -- let's say it's 1 millimeter across

<sup>60</sup> Smith Dep. (2-3-14) 779:5 to 779:8.

<sup>61</sup> ETH.MESH.00349508 at 9510.

<sup>62</sup> ETH.MESH.04941016.

<sup>63</sup> ETH.MESH.00584175 (Ex. T-3583); ETH.MESH.00584179 (Ex. T-3581).

hypothetically. If a load is put on the mesh and it changes the pore size, that pore could be, after a load is put on it, under 1 millimeter; correct?

A: It's possible depending on the load.<sup>64</sup>

Ethicon engineer Christophe Vaihle testified that “excessive tension on the mesh would lead to the decrease in pore size that can lead to poor tissue integration . . . .”<sup>65</sup> Ethicon has done nothing to change the mesh and continues to promote and sell the product with the same, heavy weight, thick filament “Old Construction 6 mil” mesh that they have been selling since 1974 (Prolene), despite what Ethicon considers to be “revolutionary” advancements in polypropylene mesh design that it brought to other pelvic floor polypropylene mesh products.<sup>66</sup>

In summary, for the reasons set forth above, it is my opinion to a reasonable degree of medical certainty that the Prolene polypropylene mesh in the TVT causes fibrotic bridging in the body, resulting in an increased inflammatory response leading to a multitude of injuries, including the possibility of multiple erosions that can occur throughout one’s lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, dyspareunia that can be chronic, nerve injury, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, the polypropylene in Ethicon’s TVT mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women.

Moreover, Ethicon did not inform physicians and patients that its mesh was susceptible to fibrotic bridging. Ethicon failed to warn physicians and patients that fibrotic bridging could

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<sup>64</sup> Smith Dep. (2/3/2014) 816:5 to 816:15.

<sup>65</sup> Vaihle Dep., (6/20/13) 224:10-226:21.

occur leading to painful erosions, recurrent, late infections, nerve injury and the need for mesh removal. By failing to do so, Ethicon did not adequately warn physicians about these important risks, nor by extension, provide surgeons with an opportunity adequately to discuss these risks with their patients.

### 5. Mesh Contracture/Shrinkage

Mesh contracture or shrinkage is an event that takes place after the implantation of mesh and relates to the wound healing process that occurs after the surgical trauma of implanting a foreign body made of polypropylene in the sensitive tissues of the vagina and pelvis. By 1998, polypropylene mesh was known to contract or shrink 30-50%.<sup>67</sup> These findings were later confirmed in numerous papers, such as those by W. Cobb and his colleagues – one of whom was Dr. Henniford (referenced above).<sup>68</sup> This also showed that heavier weight meshes like TVT led to greater amounts of contraction. The works of Cobb and Klinge/Klosterhalfen have been referenced in numerous Ethicon documents. Contraction or shrinkage has been shown to draw nerves close to the midurethral sling mesh both in the transobturator application<sup>69</sup> and for retropubic application.<sup>70</sup> Furthermore, contraction or shrinkage is closely related to the pore size and weight of the mesh. Small pore, heavy weight mesh leads to fibrotic bridging which leads to scar plates, mesh encapsulation and shrinkage or

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<sup>66</sup> ETH.MESH.03905968; *see also* Prolift +M CER (“As the mass of a mesh implant is reduced and the pore size is increased, the surface area exposed to the host is reduced, and the foreign body reaction to the implant is reduced.”).

<sup>67</sup> Klinge, U, *Shrinking of Polypropylene Mesh in Vivo: An Experimental Study in Dogs*, Eur J Surg 1998, 164:965-969.

<sup>68</sup> Cobb, W., et al., *The Argument for Lightweight Polypropylene Mesh in Hernia Repair*, Surgical Innovation 2005, 12(1):T1-T7.

<sup>69</sup> Corona, R., et al., *Tension-free Vaginal Tapes and Pelvic Nerve Neuropathy*, J Min Invas Gynecol 2008, 15:3 262-267; Parnell, B.A., et al., *Genitofemoral and Perineal Neuralgia after Transobturator Midurethral Sling*, Obstet.

Gynecol 2012, 119:428-431; Jacquetin, B, *Complications of Vaginal Mesh: Our Experience*, Intl Urogyn J, 2009, 20:893-6; Tunn, R, *Sonomorphological Evaluation of Polypropylene Mesh Implants After Vaginal Mesh Repair in Women with Cystocele or Rectocele*, Ultrasound Obstetrics Gynecol 2007, 29:449-452.

<sup>70</sup> Heise, C.P., et al., *Mesh Inguinodynia: A New Clinical Syndrome After Inguinal Herniorrhaphy?*, J Am Coll

contraction of the mesh, which is compounded by the shrinkage effect associated with the normal wound healing process already occurring in the tissue.

This phenomenon of shrinkage and its relation to the design of the pores as well as the consequences to the patient were illustrated in an email by Ethicon Scientist Joerge Holste in a March 13, 2006 email discussing a paper he authored entitled “Shrinking Meshes?”<sup>71</sup> In his email, Dr. Holste states “this was our scientific statement on mesh shrinkage: Basically, small pores, heavy weight meshes induce more fibrotic bridging tissue reaction causing more mesh shrinkage during maturation of the collagenous tissue. See my presentation about biocompatibility.”<sup>72</sup> In addition, in a presentation by Boris Batke, Associate Director R&D, he states heavier-weight polypropylene mesh results in mesh contraction of 33%.<sup>73</sup> In an email dated November of 2002, related to a discussion of mesh used in a TVT product, Axel Arnaud, one of Ethicon’s medical directors, used 30% shrinkage of the mesh as a “rule of thumb.”<sup>74</sup> At an Ethicon expert meeting in Norderstedt, Germany in 2007, an Ethicon employee presented a PowerPoint entitled “Factors Related to Mesh Shrinkage” in which all of these issues were clearly laid out.<sup>75</sup>

Mesh shrinkage was known by Ethicon as early as 1998 in published work by Ethicon’s then consultants, Uwe Klinge and Bernd Klosterhalfen.<sup>76</sup> They noted in these early papers that all polypropylene meshes shrink 30-50%. This was restated in later works by W Cobb and his

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<sup>71</sup> ETH.MESH 05446127, *supra*, n. 34.

<sup>72</sup> *Id.*

<sup>73</sup> ETH.MESH 05479717 (3/1/11 Boris Batke, Ethicon Associate Director R&D, Presentation: Ethicon Polypropylene Mesh Technology).

<sup>74</sup> ETH.MESH 03917375.

<sup>75</sup> ETH.MESH. 02017152 (Nordestadt Expert’s meeting 2007); ETH.MESH.01782867 (Factors Related to Mesh Shrinking).

<sup>76</sup> Klinge U, Klosterhalfen B, Muller M, Ottinger A, Schumpelick V. Shrinking of Polypropylene Mesh in vivo: An Experimental Study in Dogs. Eur J Surg. 1998; 164; 965-969

colleagues<sup>77</sup>--one of which was Dr. Heniford (referenced above). The words of Cobb and Klinge/Klosterhalfen have been referenced in numerous Ethicon documents and thus, Ethicon was well aware of these findings regarding the shrinkage or contraction of polypropylene meshes in vivo. Ethicon was further aware that heavier weight meshes led to greater amounts of contraction. And, notably, Ethicon equated the tissue reaction in the abdomen to heavyweight mesh to the tissue reaction in the pelvis to heavyweight mesh in marketing materials, professional educational materials and regulatory materials.

It is my opinion to a reasonable degree of medical certainty that as a result of work with internal and external experts and consultants in the late 1990s, multiple internal documents and articles, and the scientific literature as a whole, that Prolene mesh used in TVT not only could, but would shrink and contract, and that this shrinkage could lead to painful complications in women implanted with TVT, such as multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, chronic dyspareunia, nerve injury, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others.

As a result, the polypropylene in Ethicon's TVT mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women, and Ethicon failed to warn physicians and patients of the possibility of shrinkage and contraction and the adverse outcomes that could occur as a result.

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<sup>77</sup> ETH.MESH.07455220.

**6. Fraying, Particle Loss, Roping and Curling, Deformation and Loss of Pore Size**

Ethicon designed the TVT mesh such that, when stress was put on the mesh, particles would separate from the mesh – this was called fraying or linting.<sup>78</sup> One of Ethicon’s engineers described this as a “defect” that resulted from the method of cutting the mesh: “The mesh frayed is the reverse defect of the mesh features (elasticity of the mesh is one of the commercial arguments to market the TVT).... [T]he root cause of this phenomenon are known: the way to cut the mesh (blade cutting). If we change the way to cut the mesh (ultrasonic cutting or laser cutting) it seems we can limit the mesh frayed defect significantly....”<sup>79</sup>

As early as 2000, Ethicon’s engineers documented that particles from TVT Prolene mesh fell into women’s tissues as a result of the tape edges being damaged during sheath removal.<sup>80</sup> In April 2001, Dr. Alex Wang, “one of the most experienced TVT users in the world,” reported problems with frayed mesh and uneven tape width.<sup>81</sup> Although the issue was described as “serious” and as requiring “urgent attention and solution,” Ethicon Medical Director, Dr. Martin Weisberg, simply concluded that the deformity in the mesh would be unlikely to have any clinical significance. Dr. Weisberg testified that although he did not actually know whether frayed mesh leading to particle loss would have clinical implications, he does not recall whether he or anyone else at Ethicon studied the issue.<sup>82</sup> Just a few months later, however, Ethicon received a complaint by an experienced surgeon regarding a patient who experienced vaginal wall erosion following a TVT procedure which was first noted by her

<sup>78</sup> Weisberg Dep. (5/31/13) 461:7-462:3 (“Q. So engineers within the company knew that fraying of the product was inherent in the design? A. Yes.”).

<sup>79</sup> ETH.MESH.01813975 at 2 (Ex. 3160/3587).

<sup>80</sup> ETH.MESH.01317515 (7/12/00 Preventia TVT-2 Risk Analysis Procedure/Tensioning Frayed Mesh/Particle Loss). at 7523.

<sup>81</sup> ETH.MESH.03905472 (6/4/01 Emails from Wang, A. re TVT Recommendation for Ethicon Study of Fraying/Particle Loss).



husband during intercourse.

According to the surgeon, “the tape appeared frayed and tiny fibers were protruding through the vaginal wall.”<sup>83</sup> In November 2003, Dr. Weisberg reported that there had been a total of 58 complaints of fraying with TVT since introduction of the device in 2000. He observed that the following occurs when the mesh frays: “[T]he mesh elongates in places; the mesh narrows in places; and small particles of Prolene might break off ... and that [s]tretching of the mesh increases the probability of fraying.”<sup>84</sup> Once again, however, Dr. Weisberg concluded that “since fraying does not affect the safety and efficacy of the TVT device, it has been determined not to pursue any corrective actions at this time.”<sup>85</sup> Dr. Weisberg confirmed during his deposition that no corrective action was taken and, although he did not know whether Prolene particles could elicit a chronic foreign body response, he does not recall whether he or anyone else at Ethicon investigated the issue.<sup>86</sup>

In 2004, Ethicon continued to receive complaints from surgeons about fraying and “brittle” mesh and particles falling into the operating field.<sup>87</sup> One of the company’s “most urgent customers,” Swiss surgeon Dr. J. Eberhard, wrote the following: “Already at the operation it is embarrassing to see how the tape is crumbling. But it gets worse if there is stretch on the tape.... I can’t understand that no one will solve that problem for such a long time. As the latest, as the tape has becoming blue, everyone has realized that the quality of the tape is terrible.”<sup>88</sup>

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<sup>82</sup> Weisberg Dep. (5/31/13) 469:23-470:16.

<sup>83</sup> ETH.MESH.02621559 at 2276 (Ethicon Issue Report TVT Retropubic 2001 Open Date Between 01- Jan-2001 and 31-Dec-2001).

<sup>84</sup> ETH.MESH.00541379 (11/18/03 Memo from Weisberg re Mesh Fraying for TVT Devices Inadequate Testing).

<sup>85</sup> *Id.*

<sup>86</sup> Weisberg Dep. (5/31/13) 469:23-470:16.

<sup>87</sup> ETH.MESH.00863391 at 3392 (2/27/04 Emails from Smith, D. re 2 TVT Complaints Concerning Allegedly Brittle Mesh).

<sup>88</sup> ETH.MESH.02180833 (11/12/04 Letter from Prof. Dr. Eberhard (translated)); ETH.MESH.02180828 (11/12/04

Dan Smith, the Lead Engineer on TVT lamented the particle loss that was revealed when the mesh was dyed blue: “This is not going away anytime soon and competition will have a field day, major damage control offensive needs to start to educate reps and surgeons UPFRONT that they will see BLUE shit and it is OK.”<sup>89</sup> Indeed in November 2004, one of the “top 3 complaints” included “Mesh frayed.”<sup>90</sup> Once again, however, Ethicon decided to take no corrective action.<sup>91</sup> Instead, sales representatives were instructed to reassure their doctors that, “Prolene is proven to be inert,” the “particles will not cause any problem,” and to “be proactive” because “the competition will try to target this!”<sup>92</sup> Physicians were told the particles are “non- reactive” and that fraying does not affect the safety or efficacy of the device.<sup>93</sup> In fact, it has consistently been Ethicon’s position that frayed mesh and resulting particle loss as well as roping, curling and deformation of the mesh do not create a safety risk and have no clinical significance.<sup>94</sup>

However, as noted above, Ethicon never tested whether the particles would cause pain in women.<sup>95</sup> Moreover, Ethicon never specifically tested whether the particles, or frayed, curled shrunken and deformed mesh, would cause pain when in close proximity to the pelvic and vaginal nerve bundle and muscles. An independent investigator, Dr. Pariente, did and published a study that concluded that “the very high particle shedding for both Sparc (AMS)

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Telefax from Sibyll, B. re Prof. Dr. Eberhard).

<sup>89</sup> ETH.MESH.00863391.

<sup>90</sup> ETH.MESH.01813975 (Ex. T-3160 / T-3587).

<sup>91</sup> ETH.MESH.02180826 (11/12/04 Email from Menneret, D. re Mesh Fraying: Dr. Eberhard Letter).

<sup>92</sup> ETH.MESH.00865322 (3/2/04 Email from Bell, S., Ethicon Marketing Director Europe to Sales & Marketing Team re Reminder on Blue Mesh – Frayed Mesh/Particle Loss).

<sup>93</sup> ETH.MESH.03535750 (10/12/2005 Hunsicker, K., Ethicon Clinical Operations Regional Manager, Presentation: *Investigator Initiated Study Process – Inadequate Testing*).

<sup>94</sup> ETH.MESH.00541379, *supra*, n. 58; ETH.MESH.00858252 (2004 Memo from London Brown, A. re Mechanical Cut v. Laser Cut Mesh Rationale).

<sup>95</sup> Trial Testimony of Piet Hinoul, Batiste v. Ethicon, page 26-28.

and TVT (Ethicon) may be of significant long term clinical concern in some quarters.”<sup>96</sup> In addition, Ethicon collected data from physicians who informed Ethicon that particles could, indeed, cause pain and dyspareunia.<sup>97</sup> Moreover, Ethicon medical director Piet Hinoul testified the particles that fall off the mesh create inflammation and inflammation can cause pain.<sup>98</sup> Although Ethicon claims that its own internal testing shows approximately 1% particle loss with TVT,<sup>99</sup> Dr. Pariente’s study demonstrated TVT particle loss as high as 8.5% - 10 times higher than most of its competitors.<sup>100</sup> In addition, Ethicon’s April 2006 Clinical Expert Report on Laser Cut Mesh suggested there was a decrease in particle loss with laser cut mesh and this “decrease would lead to less non-functioning material left in the tissues.”<sup>101</sup> It cannot be disputed that the greater the nonfunctioning material left in a patient’s tissues, the greater the surface area of polypropylene the patient is exposed to, and the greater the inflammatory responses and the greater the foreign body response. As discussed above, the long term consequences of this chronic foreign body reaction and inflammatory response can be, among other things, chronic pain, lifelong risk of erosions, dyspareunia and failure of the device. If the individual flakes work their way through the vaginal mucosa, this can lead to dyspareunia and/or painful intercourse for the partner as noted in the complaint received by Ethicon back in 2001 referenced above. The larger the surface area the greater the risk associated with vaginal mesh. Finally, detached flakes of polypropylene may migrate into the vasculature or lymphatics and cause problems remote from the pelvis. For these reasons, Ethicon should have

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<sup>96</sup> ETH.MESH.01221055 (Pariente, J-L, *An independent biomechanical evaluation of commercially available suburethral slings*, Issues in Women’s Health 2003).

<sup>97</sup> ETH.MESH.05644163 at 4166 (Dr. Hilton, one of Ethicon’s principal investigators in the TVT v. Burch trial, informed Ethicon that: “The small particles migrate and cause pain during intercourse.”).

<sup>98</sup> Trial Testimony of Piet Hinoul, *Batiste v. Ethicon*, page 26-28.

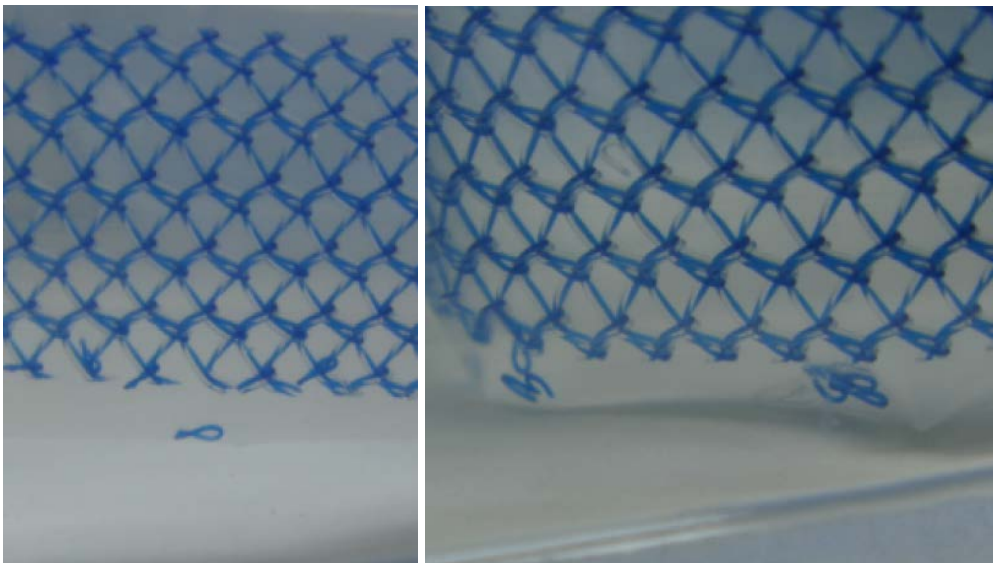
<sup>99</sup> ETH.MESH.000585802; ETH.MESH.00585842; ETH.MESH.00585823 06/27/06 (Email from Kammerer, G. re GY: \*\*\*URGENT\*\*\* French STANDARD ON TVT & MESHES (COMMENTS REQUIRED)).

<sup>100</sup> ETH.MESH.01221055, *supra*, n. 67; ETH.MESH.00585842 (6/12/06 Email from Kammerer, G. re TVT LCM –

<sup>101</sup> ETH.MESH.00167104 at 7109.

used a mesh without a fraying and particle loss defect when selling its TVT for permanent implant in a woman's vaginal tissues.

Ethicon continued to receive complaints related to particle loss from the mechanically cut mesh in the TVT. In 2010, customers complained that they were seeing pieces of mesh in the unopened packages. Ethicon employees initially responded that "No, this is not nor do we recommend using the product." Pictures from Ethicon's complaint file reveal particles of the mesh that have begun to break off from the mesh inside the package.<sup>102</sup>



Nine packages with particles of loose mesh were returned to Ethicon for analysis. I have requested to examine these products, but have been told that Ethicon has discarded these products.<sup>103</sup> Ethicon employees later reversed their position on the mesh particles stating that: "mesh particles of this size are common with the manual cutting process and are within our specifications. The product is safe to use."<sup>104</sup> This conclusion seems to be at odds with internal

<sup>102</sup> ETH.MESH.13204508.

<sup>103</sup> Letter from Ben Watson to Andrew Faes, April 16, 2015; Letter from Andrew Faes to Ben Watson, March 25, 2015.

<sup>104</sup> ETH.MESH.13226457.

manufacturing documents indicating that nearly 2,000 TVT and other mesh products were rejected because of foreign matter in the product or packaging during the month of March, 2010 alone at Ethicon's Neuchatel manufacturing facility.<sup>105</sup> Ethicon's conclusion that the products were safe to use does not appear to be a result of any scientific or engineering study of the returned products, but rather the conclusion of Ethicon Medical Director David Robinson that "...the possibility for the tiny tape fragments observed... ... to cause adverse consequence in a patient... ... should be considered remote. The presence of tiny tape fragments in the product package is not expected to change the product safety profile."<sup>106</sup> It is my opinion to a reasonable degree of medical certainty that this conclusion is incorrect and not supported by any study or clinical evidence gathered by Ethicon. In fact this conclusion is belied by the fact that Ethicon told the same physicians who complained about the particles that they may wish to consider TVT mesh manufactured with a laser cutting process that does not result in tiny mesh particles within the package.<sup>107</sup> Because of dangers associated with loose particles, fraying and deformed mesh, described more fully below, the mesh from this TVT mesh posed unreasonable dangers to women and Ethicon should have never allowed the mechanically cut mesh in the TVT to be offered for sale for implantation in women.

In addition to fraying and particle loss, the mechanically cut meshes used in TVT has also been shown to rope, curl and deform when under tension. In 2006, an Ethicon Engineer, Gene Kammerer, made a presentation that clearly showed each of these defects in the mechanically cut mesh. These photos clearly show particle loss, fraying, degradation, roping and deformation when the mechanical cut mesh was stretched and compared to TVT Laser

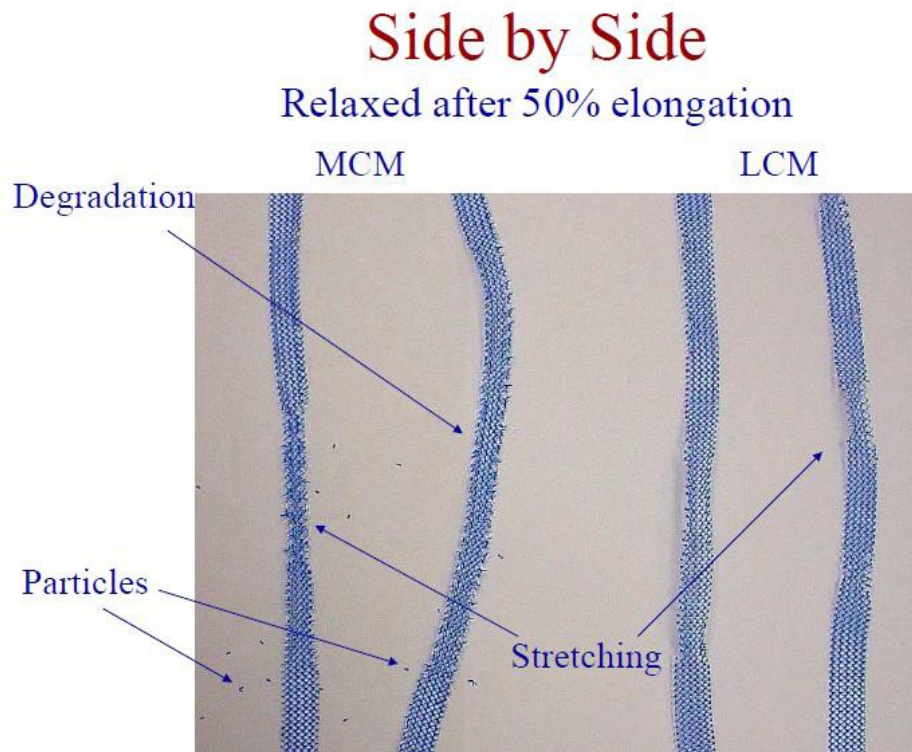
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<sup>105</sup> ETH.MESH.13907354-55.

<sup>106</sup> ETH.MESH.04101014.

<sup>107</sup> ETH.MESH.13226457.

Cut.<sup>108</sup>



As noted these photos show mesh after 50% elongation. I have read depositions of Ethicon personnel claiming this is not a realistic elongation seen with mesh. However, Ethicon's engineer who took the photos, Gene Kammerer, explained that he had experienced it himself in testing:

The link between the elongation percent, not force, and the integrity of the mesh is this. During the operative procedure as the surgeon removes the protective sheath from the mesh, the mesh stretches or elongates. It is my experience, after viewing many surgical procedures and performing numerous procedures on cadavers myself, that the mesh stretches approximately 50% at the maximum. There is also additional stretching that occurs if the surgeon elects to do an adjustment on the position of the mesh under the urethra. It is these two occurrences which produce the majority of the particle loss and loss of the integrity of the construction of the mesh.<sup>109</sup>

Again, Ethicon claimed that these problems with the mesh did not have any clinical

<sup>108</sup> ETH.MESH.08334245.

<sup>109</sup> ETH.MESH.00584811.

significance despite the fact that surgeons were complaining.<sup>110</sup> However, Ethicon's own internal documents demonstrate that this is not true. According to Ethicon's Failure Modes documents, the loss of pore size due to mesh narrowing or deformation can lead to urinary retention or erosion. Ethicon's own dFMEA from 2006 shows that the hazards of curling/roping, frayed edges and inadequate pore size of mesh can lead to the harms of erosion, recurrence, and pain.<sup>111</sup>

When discussing the dFMEA for Laser Cut Mesh, Former Medical Director, David Robinson, agreed that pore size of both the Laser Cut and Mechanically Cut mesh "[c]ould reduce, the tissue might not encapsulate . . . the tissue might not grow through the mesh. It can become encapsulated and then it could cause . . . a rejection of the mesh."<sup>112</sup> And, Dr. Robinson testified that rejection of the mesh can lead to erosion.<sup>113</sup> These changes in the mesh may lead to erosion or pain for women with the deformed mesh implanted in their bodies. Further, according to Ethicon, this curling, roping or narrowing of the mesh may also cause urinary retention in addition to erosion and pain.<sup>114</sup>

In fact, I have witnessed the same type of roping and narrowing of TVT when I placed them myself. I see the deformed and roped mesh when I remove them. This localized pressure under the urethra leads to complications like, among others, urinary retention, chronic pain, dyspareunia and erosions. In addition, I have reviewed Ethicon TVT training videos that show the exact problem discussed about related to deformation and roping of the "tape" under the urethra.<sup>115</sup> Finally, according to Ethicon's Dan Lamont, it chose to continue to sell

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<sup>110</sup> ETH.MESH.00440005; ETH.MESH.00302390 (TVT-Base & TVT Review for Laser Cut Mesh (LCM) Risk Analysis).

<sup>111</sup> ETH.MESH.01218019.

<sup>112</sup> Robinson Dep. (9/11/13) 1070:23-1072:25.

<sup>113</sup> *Id.*

<sup>114</sup> Robinson Dep. (9/11/13) 1079:3-4-1081; 1081:9-13; 1083:8-18; ETH.MESH.01218019.

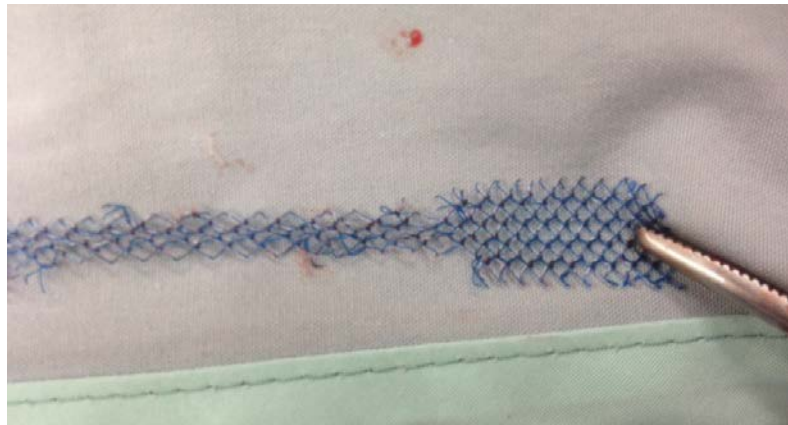
<sup>115</sup> ETH.MESH.PM.000004 (TVT Retropubic Implantation Video).



“mechanically cut mesh despite knowing that it had the potential for degradation, particles floating around in women’s bodies, stretching, and roping . . .”<sup>116</sup> Lamont admitted that the fraying of the mesh was a “defect” of the mesh.<sup>117</sup>

Not surprisingly, Ethicon continues to receive complaints related to the mechanical cut mesh used in TVT fraying, roping and curling. Recently, the highest volume user of TVT products in Canada, Dr. Kenny Maslow, complained to Ethicon that the mesh used in TVT would fray down to a thin fiber even with “very little tension applied to the sling.”<sup>118</sup>

Dr. Maslow included a picture of the frayed mesh used in TVT when he reported the issue to Ethicon.



Another feature of mechanically cut mesh is its sharp edges as shown on this photo:<sup>119</sup>

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<sup>116</sup> Lamont Dep. (9/11/13) 30:18-24.

<sup>117</sup> Lamont Dep. 9/11/13) 15:16-16:10.

<sup>118</sup> ETH.MESH.12910023.

<sup>119</sup> ETH.MESH.09656795.





While Ethicon states that these sharp edges are part of the intended “velcro” effect of mesh, it was a feature about which Ethicon had received complaints tied to injuries and erosions. For example, during on market research test with physicians, it was reported:

The surgeon felt that the MCM strips was elastic but with "hairs" on the edges and that it scratched with abrasive texture scraping (like the Scotch -Brite™ pads), furthermore a lot of particles were released and a rope/string effect could occurred if an excessive force was applied.<sup>120</sup>

In fact, when one agency recognized a spike in erosions, it inquired whether this was a result of “the cut ends of the tape appear to be sharper and more likely to cut tissue.”<sup>121</sup> A sentiment shared by some physicians and reported to Ethicon:

Basically, he thinks that erosions due to the TVT mesh are underestimated in reports. The reason is that in order to recognize them, a very careful vaginal examination is needed. Most of the time, a "hidden" erosion is asymptomatic and neither the patients nor their sexual partner if any complain. But it might happen that a patient may complain. He believes that erosion are due to the sharp edges of the mesh. He wanted to suggest that we add to the mesh edges a kind of seam that would help preventing erosion.<sup>122</sup>

Dr. Axel Arnaud responded that Ethicon did not want to modify its mesh (even if it caused

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<sup>120</sup> ETH.MESH.06696589.

<sup>121</sup> ETH.MESH.00330760.

erosions) because Ethicon did not want to lose the marketing edge of using the Ulmsten/Nilsson data. He wrote:

I also indicated that we want to be very careful with any modifications of our tape since a change in the mesh would obsolete all the long term clinical results we have about the procedure.<sup>123</sup>

However, the market pressure on Ethicon to create a laser cut mesh without particle loss, roping and deformation became very strong. Paula Evans, Gynecare European Marketing Manager, described the situation as "France is in a recovery mode, Germany is hemorrhaging business ... Without laser cut, there is the real risk that more business will be lost." (sic).<sup>124</sup> Hence, the laser cut mesh project went forward presumably in an effort to address the chronic problems with particle loss, fraying, sharp edges and elongation seen with mechanically cut mesh.<sup>125</sup>

During early development of laser cut, Ethicon acknowledged that mechanical cut mesh and laser cut mesh were two separate mesh products and to imply otherwise would be misleading. In December 2005, Kevin Mahar described the marketing strategy "...KEEP selling regular TVT (the 'Colonel's Original Recipe') to those customers that want/love it...and KEEP going forward with 8 years of data, etc with the original recipe ... We do not mislead them that this is the same product..."<sup>126</sup> In discussing that document, Dr. Robinson verified that Mahar was referring to the mechanically cut mesh as the Colonel's Original Recipe:

Q: He writes, "While we" -- "While we would work with our agency to get this right, my thoughts are that we keep selling regular TVT," meaning

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<sup>122</sup> ETH.MESH.03911107 (Axel Arnaud reporting his interview with Professor Hausler).

<sup>123</sup> *Id.*

<sup>124</sup> ETH.MESH.04985249.

<sup>125</sup> ETH.MESH.00301741 (11/21/05 Email from Lamont, D. re !!!!GREAT NEWS FOR TVT LASER CUT MESH!!!! -Frayed mesh/particle loss); ETH.MESH.00394544 (2/01/06 Global Regulatory Strategy - GYNECARE TVT - Laser Cutting Project); Weisberg Dep. (5/31/13) 487:13-488:7.

<sup>126</sup> ETH.MESH.00687819 (Ex. T-3164).

- the mechanically-cut mesh, right?
- A. Yes.
- Q. "(The Colonel's 'Original Recipe') to those customers that want/love it." Right?
- A. Yes.
- Q. Talking about a piece of plastic that is permanently implanted in a woman's body as the "Original Recipe," right?
- A. That -- yes, that's correct.<sup>127</sup>

Ethicon initially decided that particle loss, elongation curve and flexural rigidity data on laser cut would not be required because they were not "critical to quality." In fact, this news was celebrated as "!!!!GREAT NEWS FOR TVT LASER CUT MESH!!!!" and "less work for all of us."<sup>128</sup> However, because Ethicon wanted to continue to claim the marketing benefit of the Ulmsten/Nilsson series, marketing determined that some testing was needed. This was described as a way to protect the "clinical heritage" of the mesh:

Marketing Need: Keep clinical heritage intact.... In order to continue to claim the use of 7-year data and all clinical studies, the MCM and LCM needed to show similar properties with the physical properties being used as a proxy for the clinical needs.<sup>129</sup>

Ultimately, Ethicon did not end up telling doctors that the mechanically cut mesh and the laser cut mesh are essentially the same, a decision that has kept doctors in the dark about the defects inherent in the mechanically cut TVT mesh, and has led to continued harms and hazards to women. In my opinion as a physician, Ethicon's decision to continue to market and sell the mechanically cut mesh, with all of its defects, and the decision to market the improved laser cut mesh as virtually the same as the old construction (Prolene) mesh, was clearly a decision by Ethicon to put profits before patient safety. In summary, for the reasons set forth above, it is my opinion to a reasonable degree of medical certainty that the Prolene

<sup>127</sup> Robinson Dep. (7/25/13) 585:12-23.

<sup>128</sup> *Id.*; ETH.MESH.00584291 (2/15/06 Email from Flatow, J.re DVer protocol for particle loss).

<sup>129</sup> ETH.MESH.00858252; *see also* ETH.MESH.00526473; ETH.MESH.02248778 (Kammerer PPT); Hellhammer Dep. (9/11/13) 120-121.

polypropylene mesh in the TVT has several characteristics that make it improper for use in the vaginal canal including particle loss, fraying, roping, curling, deformation and loss of pore size. These unwanted characteristics can lead to, among other things, an increased inflammatory response (particle loss and fraying) and/or increased pressure on the urethra (roping or curling) or loss of pore size (roping or curling), and can lead to a multitude of injuries, including such as multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, the polypropylene in Ethicon's TVT mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women.

Moreover, Ethicon did not inform physicians and patients that its mesh was susceptible to these physical deformations that could lead to painful erosions, recurrent, late infections and the need for mesh removal. Nor did Ethicon inform physicians that laser cut mesh had materially different mechanical properties than mechanically cut mesh. By failing to do so, Ethicon did not adequately warn physicians about these important risks, nor by extension, provide surgeons with an opportunity to discuss these risks with their patients.

- B. Ethicon knew that the old construction mesh (Prolene) was not appropriate for use in its TVT device as early as 1998, but failed to modify/change the mesh to a larger pore, lighter weight mesh that would not deform, fray, lose particles, rope, curl, degrade, cause excessive foreign body reactions, and cause excessive shrinkage/contraction because of its economic interest in maintaining its competitive advantage in the MUS market and, therefore, Ethicon put profits before patient safety.**

As stated above, Ethicon knew from the time it launched the TVT with the

mechanically cut mesh that it was defective in multiple respects. This is true because the TVT Prolene mesh was known to be made from heavyweight 6 mil fiber and a construction that allowed for mesh curling, roping, fraying, zipping, particle loss, and sharp edges. In fact, beginning in 1998, Ethicon had already established a “mesh improvement project” in order to improve the mesh. Despite the fact that the project yielded an improved mesh, Ethicon never incorporated those improvements into the TVT.

As early as May of 1997, Ethicon knew that the Prolene mesh was not ideal for use in vaginal tissues.<sup>130</sup> In fact, Ethicon knew of a case at that time where a patient had been treated with Prolene mesh, which protruded through the vagina, requiring excision of the mesh. Ethicon knew that the ideal mesh for use in the vagina should not have any fraying or spiky edges, needed to have large enough pores to encourage in-growth, and should have a low mass density to minimize foreign body reaction.<sup>131</sup> Ethicon then embarked on a project to improve the Prolene mesh used in the TVT product and Ethicon’s hernia products. Among the characteristics they sought to improve were the product curling, zipping and unraveling of the mesh after cutting, and crumbling of the mesh.<sup>132</sup> Ethicon noted that if the Prolene mesh was pulled in one direction, the mesh would curl up into a tube, and the mesh would remain in a rolled condition even after the force of the pulling was no longer on the mesh.

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<sup>130</sup> ETH.MESH.12006257

<sup>131</sup> ETH.MESH.12006257

<sup>132</sup> ETH.MESH.09264945

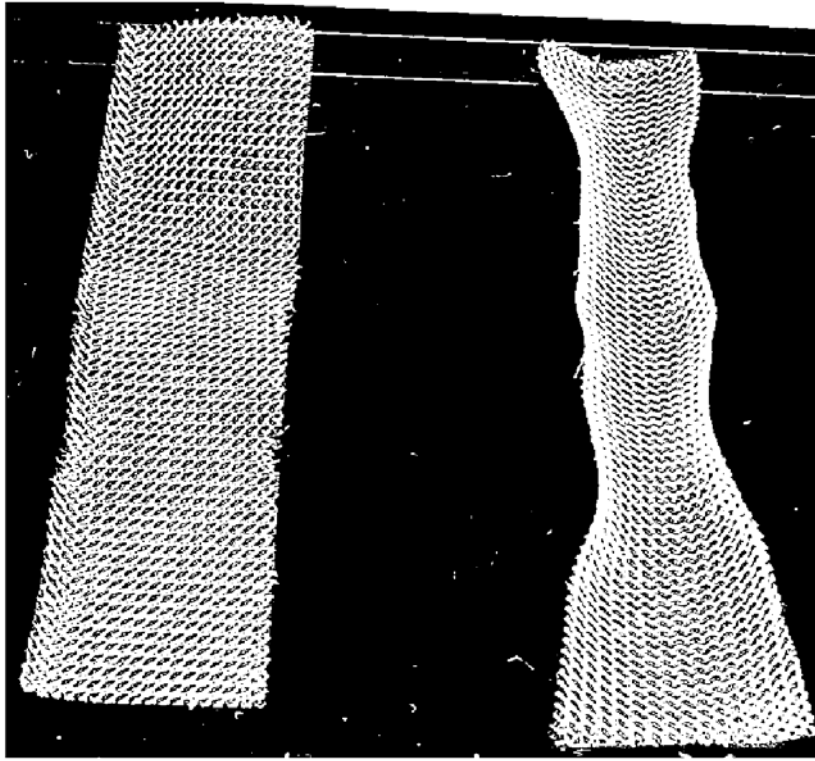


Figure 1 – Control mesh sample before and after the application of the force. A clear picture of mesh curling results.

Ethicon also referred to the original construction 6 mil Prolene mesh as a mesh that was known for its “bad” curling quality.<sup>133</sup> Ethicon ultimately changed the flat Prolene mesh used for hernia repair to address these issues, making changes to the construction of the mesh to address the bad curling quality of the mesh, and at the same time, changing to a lighter weight, 5 mil mesh construction.<sup>134</sup> The change in the mesh construction also made the mesh less likely to fray and lose particles.<sup>135</sup> Despite Ethicon’s original intent to incorporate the new construction material which was lighter weight and had improved resistance to curling, fraying, and particle loss,<sup>136</sup> Ethicon continued and still continues to use the original, old, old

<sup>133</sup> ETH.MESH.02182844, ETH.MESH.00946834.

<sup>134</sup> ETH.MESH.00782152.

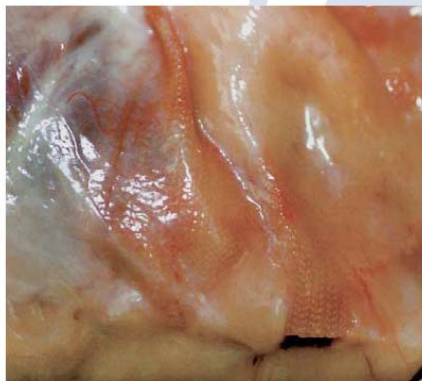
<sup>135</sup> ETH.MESH.020008684.

<sup>136</sup> ETH.MESH.09264884.



heavyweight 6 mil construction mesh for the TVT products.<sup>137</sup>

The flaw in the construction of the TVT heavyweight Prolene mesh which allows it to curl into a tube after tensioning or pulling on the mesh and not return to its original shape, combined with the heavyweight and small pore nature of the mesh, causes the mesh to fold up and become hard post-implantation. Ethicon continued to be aware of this continuing defect in the mesh well after the Prolene mesh improvement project was completed and the company changed the construction of its Prolene hernia mesh.<sup>138</sup> Ethicon was also aware that lightweight materials were less likely to fold up post implantation and integrated better with surrounding tissues,<sup>139</sup> but continued to use the heavier 6 mil fibers. The lightweight materials were also much better at resisting crumpling and less likely to have sharp edges during tissue integration.<sup>140</sup>



Traditional polypropylene mesh. 90 days post-implantation. Fold development (in-vivo study)



Lightweight VYPRO\* II mesh. 90 days post-implantation. Fold-free incorporation (in-vivo study)

Ethicon continued to have problems with mesh quality in the TVT mesh after the Prolene mesh improvement project was complete, but never incorporated those changes into

<sup>137</sup> ETH.MESH.09275875, ETH.MESH.02030355.

<sup>138</sup> ETH.MESH.05918776.

<sup>139</sup> ETH.MESH.05446129.

<sup>140</sup> Ethicon Tissue Reinforcement Solutions, 8/21/2004.

the TVT mesh. After the improved construction 5 mil Prolene mesh replaced the 6 mil mesh Prolene mesh for flat hernia repair, Ethicon noted continuing problems with the Prolene mesh in the TVT, noting inconsistent tape width,<sup>141</sup> and fraying and particle loss from the TVT mesh.<sup>142</sup> Doctors reported to Ethicon that the quality of the mesh was terrible, and that particles were falling off the mesh, which was worse when the mesh was elongated.<sup>143</sup>

Even before the TVT was launched in the United States, Ethicon was looking at ways to change the existing mesh tape construction in order to improve the appearance of the mesh and to alleviate problems experienced during the manufacturing process.<sup>144</sup> Ethicon also knew prior to launching the TVT for sale in the United States that if the tape became twisted, it would reduce the effectiveness of the TVT procedure, and evaluated laser-cut samples of the TVT mesh as opposed to the mechanically cut mesh.<sup>145</sup> The project which looked at laser cutting the mesh was part of the “TVT improvement project” which began prior to the launch of the TVT in the United States. Included in the goals of the TVT improvement project were a mesh that was safer, eliminated abrasion, rough edges, and narrowing of the mesh under tension.<sup>146</sup> Ethicon evaluated feedback from surgeons who compared the Laser cut mesh to the guillotine (mechanically) cut mesh, and were told that the laser cut mesh had a more regular appearance, the mesh did not stretch as much as the current guillotine cut mesh, and there was a marked reduction in the amount of loose ends falling off.<sup>147</sup> Testing also showed that the mechanically cut mesh stretched 90% more than the laser cut mesh when force was applied to the mesh. However, despite having a laser cut mesh available which had less rough edges, less

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<sup>141</sup> ETH.MESH.12002601.

<sup>142</sup> ETH.MESH.00863405.

<sup>143</sup> ETH.MESH.02180833.

<sup>144</sup> ETH.MESH.10591870.

<sup>145</sup> ETH.MESH.12009079.

<sup>146</sup> ETH.MESH.12009262; ETH.MESH.12009276.



particle loss, and less narrowing and deformation under tension, Ethicon chose to launch the TVT in the United States with the guillotine (mechanically) cut mesh.

Ethicon did not change the Prolene mesh in its TVT device despite having better and safer options available for economic reasons. Ethicon believed that continued use of the TVT mesh gave the company an economic and competitive advantage in marketing the product because they could continue to use the existing clinical data on the product to market the device, while if the mesh was changed, the existing clinical data would be obsolete.<sup>148</sup> Dr. Brigitte Hellhammer testified that despite having incorporated the use of the lightweight, large pore Ultrapro mesh in vaginal tissues for the treatment of pelvic organ prolapse, the Ultrapro was never used by Ethicon in a device used for the treatment of stress urinary incontinence largely because the company wanted to continue to rely on the Ulmsten/Nilsson series of studies on 130 patients performed with the TVT device.<sup>149</sup> Dr. Arnaud also confirmed that the company did not want to change anything with the mesh because of the exiting clinical data on the product.<sup>150</sup> It is my opinion to a reasonable degree of medical certainty that Ethicon was negligent in failing to correct the defects in the TVT mesh as the company had knowledge of the defects and failed to correct the defects with products and solutions that were already available to the company because it put its economic interests above the safety of patients.

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<sup>147</sup> ETH.MESH.10182456.

<sup>148</sup> ETH.MESH.03911107.

**C. Ethicon's TVT's design is flawed because it cannot adequately describe, inform or explain to physicians how to properly "tension" the TVT and the mesh shrinks, contracts, ropes and curls making it impossible to tension.**

TVT stands for and has consistently been marketed by Ethicon as "Tension-free Vaginal Tape." Presumably, this means the mesh should be inserted under the urethra without tension. However, the term "tension-free" is misleading. In practice, too little or no tension results in failure to treat the underlying condition of urinary incontinence. On the other hand, as suggested by Ethicon's own internal documents, too much tension can result in serious complications such as retention and urethral erosion.<sup>151</sup> Also, as discussed above, because the mesh shrinks, contracts, ropes and curls, it is impossible or extremely difficult to properly tension the mesh.

The IFU provides little guidance on proper tensioning of the TVT. Specifically, once the tape is placed, surgeons are simply instructed to pull the needles upwards "to bring the tape (sling) loosely, i.e. without tension, under the midurethra" and to "adjust the tape so that leakage is limited to no more than one or two drops."<sup>152</sup> The IFU's Warnings and Precautions section cautions surgeons to "[e]nsure that the tape is placed with minimal tension under the mid-urethra."<sup>153</sup> Yet in the very same section, the surgeon is instructed "to place the tape tension-free in the mid-urethral position" to minimize the risk of de novo detrusor instability.<sup>154</sup> Finally, the IFU's "Adverse Reactions" section provides that "over correcting, i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction."<sup>155</sup> The IFU's conflicting instructions with regard to tensioning of the tape,

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<sup>149</sup> Deposition of Brigitte Hellhammer, MD, September 11, 2013.

<sup>150</sup> Deposition of Axel Arnaud, July 19, 2013 36:15-37:3.

<sup>151</sup> ETH.MESH.05529274; ETH.MESH.04044797; ETH.MESH.05529653; ETH.MESH.00161131.

<sup>152</sup> Eth.Mesh.05222686, emphasis added.

<sup>153</sup> Eth.Mesh.05222687, emphasis added.

<sup>154</sup> Eth.Mesh.05222567, emphasis added.

<sup>155</sup> Eth.Mesh.05222687, emphasis added.

i.e. “without tension,” “with minimal tension,” “tension-free” and “overcorrecting, i.e. too much tension” are clearly confusing and inadequate despite the fact that Ethicon knew as early as 2000 that improper tensioning could lead to complications and, therefore, the IFU needed to be “clear.”<sup>156</sup> These tension issues are compounded when the mesh contracts, shrinks and deforms as discussed above.

Ethicon recognized as far back as November 1999 that TVT tension adjustment was considered “high need” and surgeons had a hard time sticking to proposed technique.<sup>157</sup> By 2000, Ethicon recognized that excess tensioning during initial placement could create a risk of erosion.<sup>158</sup> In an email dated February 13, 2001, Medical Director Axel Arnaud wrote “there is clearly a need for standardization of the TVT procedure to avoid excessive tension on the mesh. We should aggressively work in order to develop a product and I would like to take the responsibility for this.”<sup>159</sup> In May 2002, Axel Arnaud continued to recognize the need to develop a safer device “in order to prevent excess tension of the tape.”<sup>160</sup> In 2003, Ethicon recognized that a challenge with the TVT procedure remained complications “associated with over-tensioning of the sling and the inability to obtain precise biofeedback and adjustment during and/or after the procedure.”<sup>161</sup> Indeed, Dr. Nilsson, the “father of the TVT”, discussed that the TVT done under general anesthesia with a cough test was 70% successful compared to a 85% success rate when done with local anesthesia and a cough test.<sup>162</sup>

The lack of clear direction on tensioning in the IFU is demonstrated in September 2004 emails from Sales Representative Shannon Campbell in which she writes: “What is a huge

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<sup>156</sup> Eth.Mesh.01317523.

<sup>157</sup> Eth.Mesh.05641096.

<sup>158</sup> Eth.Mesh.05529274; Eth.Mesh.04044797; Eth.Mesh.05529653; Eth.Mesh.00161131.

<sup>159</sup> Eth.Mesh.03915380.

<sup>160</sup> Eth.Mesh.03907468.

<sup>161</sup> Eth.Mesh.00259271.

<sup>162</sup> Eth.Mesh.04048515 at Eth.Mesh.0408516 7/01/08 KOL Interview: Carl G. Nilsson, Project Scion.

challenge to a rep trying to make this right, is that we really don't know what the right amount [of tensioning] is. We know this is a quick fix to the problem, but not a clinically backed solution. It's almost like trying to decide if a 8, 10, or 12 mm Hagar dialator is best for tensioning TVT with the patient under general. We learned the cough test, but relied on surgeons experience with the tensioning under general.... This has been such a gray area and everyone seems to have their own tensioning technique.” She continues: “I feel I got a little grilled over my suggestion of tensioning, yet there is no clear direction on tensioning. I’m not a rebel looking for my own way of doing this. I’m a rep trying to figure out what is best from my experience with surgeons and what I see the product doing in the OR. ...The reason for my question is to see if someone had the proper wording we need to use as rep’s that eliminates our liability with the product in the OR concerning tensioning.”<sup>163</sup>

In December 2006, Ethicon Marketing Director Allison London-Brown referred to tensioning as a “sticky” question and acknowledged that “we cannot accurately describe [tensioning] in writing.”<sup>164</sup> Meanwhile, Ethicon knew that patients were suffering from erosions and, in fact, would often blame the physician as the cause of the erosion for putting “too much tension on the device.”<sup>165</sup> At least by 2007, it seems Ethicon finally acknowledged that “TVT has never been tension free!” despite years of marketing it otherwise.<sup>166</sup> For example, in 1999, Ethicon utilized marketing pieces for “TVT Tension Free Vaginal Tape” which claimed “Tension-free Support Only When Needed” which “reduces possibility of urethral erosion.”<sup>167</sup> A 2001 marketing piece for “Gynecare TVT Tension-Free Support for Incontinence” claimed “most complications are minor and are avoidable with adherence to

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<sup>163</sup> Eth.Mesh.00864503.

<sup>164</sup> Eth.Mesh. 01784428-01784435.

<sup>165</sup> Eth.Mesh.02625055, Eth.Mesh.02627811, Eth.Mesh.02625375, Eth.Mesh.02625155.

<sup>166</sup> Eth.Mesh.06861473.

procedural technique and instructions for use.”<sup>168</sup> In 2004, during the same time period when Shannon Campbell was lamenting the problems with tensioning, Ethicon continued to promote TVT as “the leader in midurethral sling devices” for “tension-free support for incontinence.”<sup>169</sup> Even after Ethicon acknowledged that TVT has never been tension free, the company continued to market it as “Tension-free Support for Incontinence.”<sup>170</sup>

Physicians were also not informed in Ethicon’s product IFU that tension on the mesh arms decreases effective pore size and interferes with incorporation into tissue. Engineer Christophe Vailhe testified that “excessive uniaxial tension on the mesh will decrease the pore size and lead to poor tissue integration.”<sup>171</sup> In addition, Mr. Vialhe testified that “excessive tension on the mesh would lead to the decrease in pore size that can lead to poor tissue integration . . . .”<sup>172</sup> Engineer Dan Burkley also testified that once the TVT Prolene mesh is either stretched by the surgeon or stretched by in-vivo due to forces in a women’s body, it can alter the structure of the pores.<sup>173</sup>

The IFU failed to adequately instruct surgeons on the critical subject of tensioning as repeatedly acknowledged by Ethicon. Ethicon now claims that “tension-free” does not really mean tension-free, but rather, means less tension than as seen in the Burch procedure.<sup>174</sup> Yet, despite its awareness of the problems associated with tensioning, Ethicon failed to revise the conflicting and ambiguous IFU to provide adequate direction on the proper amount of tensioning even though Ethicon was fully aware that improper tensioning could lead to serious complications such as urinary retention, voiding difficulties, de-novo detrusor instability,

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<sup>167</sup> Eth.Mesh.00161444.

<sup>168</sup> Eth.Mesh.00339437.

<sup>169</sup> Eth.Mesh.00160813.

<sup>170</sup> Eth.Mesh.00164643; Eth.Mesh.00339053.

<sup>171</sup> Vailhe, 6/20/13, 224:10-226:21.

<sup>172</sup> Vailhe, 6/20/13, 224-226.

<sup>173</sup> Burkley 5/22/13 430:3-431:10.

dyspareunia, vaginal extrusion and urethral erosion. In addition, the design of the device and the mesh is problematic because it shrinks, contracts and deforms exacerbating the issues discussed above.

Ethicon failed to act as a reasonable and prudent medical device manufacturer by failing to design the TVT in a way that it could be properly tensioned and by failing to inform physicians how to properly tension TVT and that improper tension could affect the pore size of the mesh. These failures by Ethicon have resulted in numerous injuries to patients, including, but not limited to chronic pain, urinary retention, voiding difficulties, de-novo detrusor instability, dyspareunia, and vaginal extrusion and urethral erosion.

As one sales representative noted in an email to Dan Smith, the inability of Ethicon to properly communicate how to tension the TVT had safety and legal ramifications:

I feel I got grilled on my suggestion of tensioning, yet there is no clear direction on tensioning.... My goal is not to get the tape changed, yet strive to place the mesh as designed without altering it. The surgeon does own the responsibility of proper delivery and placement. The fact is, they look to us as reps to show them the proper placement techniques.

The reason for my question is to see if someone had the proper wording we need to use as reps that eliminates our liability with this product in the OR concerning tensioning.<sup>175</sup>

In my opinion, Ethicon failed to properly test the unique tensioning issues related to the TVT prior to marketing the device. Ethicon left physicians without sufficient information about how to properly remove sheaths and/or properly tension the TVT mesh in light of the lack of uniformity with tensioning and for failing to account for problems with the mesh like contraction, shrinkage and deformation when tensioning. Ethicon improperly managed the sheath/tension problem by telling individual physicians “tips and tricks” including the Surgeon’s Resource Monograph. This advice necessarily could not reach hundreds of surgeons

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<sup>174</sup>Smith 6/4/13 524:20-525:13.

who did not get the “tips and tricks” from sales representatives or Ethicon employees. Such information should have been put in the IFU. Because physicians did not have the proper information, they could not impart the information to their patients or properly consent their patients for all of the risks associated with over-tensioning mesh such as roping, curling, fraying and all of the associated injuries.

**D. Ethicon’s Prolene mesh in the TVT is not suitable for permanent implant because the Material Safety Data Sheets (“MSDS”) for polypropylene resin used to manufacture polypropylene states that polypropylene is incompatible with strong oxidizers such as peroxides which are readily found in the vagina**

According to Ethicon Medical Director, Dr. Martin Weisberg, a Material Safety Data Sheet (MSDS) is “a document that discusses the product, the composition, any potential hazards from it . . . Generally, the safety particular of products.”<sup>176</sup> As it relates to polypropylene, I have reviewed several MSDSs for polypropylene resin used to manufacturer meshes used in various pelvic floor meshes. All of the MSDSs discussed below are available to the public.

Sunoco, the manufacturer for the polypropylene resin used to manufacture Ethicon’s pelvic floor products lists the possibility that polypropylene mesh is incompatible with strong oxidizers. This is documented by the Sunoco MSDS<sup>177</sup> from April 13, 2005 which states in relevant part:

**10. STABILITY AND REACTIVITY**

**• INCOMPATIBILITY**

The following materials are incompatible with this product: Strong oxidizers such as chlorine, peroxides, chromates, nitric acid, perchlorates, concentrated oxygen, sodium hypochlorite, calcium hypochlorite and permanganates. Chlorine; Nitric acid;

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<sup>175</sup> ETH.MESH.00864503.

<sup>176</sup> Weisberg Dep. (8/9/13) 909:2-9.

<sup>177</sup> ETH.MESH.02026591 at 6591-6595.

This warning is important because it states what the polypropylene in the TVT is incompatible with strong oxidizers like peroxides, which is particularly important because the vagina is a natural and ready source of peroxides. In fact, the vagina is a ready source of hydrogen peroxide production. In a paper titled, "The in vitro effects of hydrogen peroxide on vaginal microbial communities,"<sup>178</sup> the amount of hydrogen peroxide produced by the lactobacillus species is reported. The paper states, "Hydrogen Peroxide reached concentrations of from 0.05 to 1.0 mM, which under intensive aeration increases even up to 1.8 mM." This work confirmed the earlier research in the paper titled, "Hydrogen peroxide produced by Lactobacillus species as a regulatory molecule for vaginal micro-flora."<sup>179</sup> "The human body also contains other agents, such as hydrocarbons and various bacteria that impacts the MSDS discussed above and the warnings contained therein."<sup>180</sup>

The Prolene MSDS indicates that if you put the polypropylene used to make the TVT mesh in an environment with peroxides, it will start to break down. Given the information available to Ethicon concerning the dangers of polypropylene coupled with the warnings and other contents of the MSDSs and related documents, at a minimum, Ethicon should have conducted clinically relevant testing to determine if naturally occurring conditions in the vagina could cause polypropylene used in the TVT to alter inside a woman's pelvis (as well as

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<sup>178</sup> M Strus in FEMS Immunol Med Microbiol, 2006 October; 48(1:56-63).

<sup>179</sup> Med Dosw Microbiol. 2004;56(1):67-77.

<sup>180</sup> HB Moon, "Occurrence and accumulation patterns of polycyclic aromatic hydrocarbons and synthetic musk compounds in adipose tissues of Korean females" 2011; "Determination of volatile purgeable halogenated hydrocarbon in human adipose tissue and blood stream," from Bulletin of Environmental Contamination and Toxicology Volume 23 Issue 1 pp 244 – 249 published in 1979; Environmental Health Perspective's, Vol. 60 pp. 127-131, Henry Anderson, "Utilization of Adipose Tissue Biopsy and Characterizing Human Halogenated Hydrocarbon Exposure", N. Das, Journal Biotechnology Research International 2010, Vol 2011, Article ID 941810 titled, "Review Article: Microbial Degradation of Petroleum Hydrocarbons Contaminant: An Overview", "Health, Safety and Environment Fact Sheet: Hazardous Substances from CAW/TCA." (www.caw.ca) August 2011, D. Lithner, 2011, entitled "Environmental and Health Hazards of Chemicals in Plastic Polymers and Products", University of Gothenburg.



other complications). If so, what materials are released into the body as a result, and what impact would those materials have on the body. The fact that the mesh in the TVT is susceptible to breaking down when in contact with peroxides makes it an unsuitable material to be placed in the vagina for the reasons discussed above. At the very least, Ethicon should have disclosed this information to physicians and patients considering use of their pelvic mesh.

Despite the warning in the MSDS for the polypropylene resin used to manufacture the TVT mesh cautioning against contact with strong oxidizers such as peroxides, there is no evidence that Ethicon tested the mesh to see if the peroxides in the vagina broke it down or informed surgeons about this important information contained in this or various other Manufacturer Safety Data Sheets (MSDS) regarding the use of polypropylene.

The fact that the MSDS for the TVT mesh warned against contact with strong oxidizers such as peroxides is information that a doctor would want to consider before implanting a permanent device in a woman's body for the rest of her life as substances in the vagina could cause the breakdown of the product, yet there Ethicon never informed doctors about the warning in the MSDS. As a result, Ethicon failed to act like a reasonable and prudent medical device manufacturer.

**E. Ethicon's Prolene mesh is not suitable for permanent implant because the toxicity testing of the polypropylene mesh revealed that it was cytotoxic;**

Cytotoxicity means toxicity to the cells causing cell injury or death.<sup>181</sup> In a May 26, 2000, Ethicon Memo titled "Review of biocompatibility on the tension-free vaginal tape (TVT) system for compliance to FDA,"<sup>182</sup> the review contains a "Cytotoxicity Risk Assessment for the TVT (Ulmsten) Device" from August 8, 1997.<sup>183</sup> The Cytotoxicity Assessment states

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<sup>181</sup> Robinson Dep. (9/11/13) 1091:11-21.

<sup>182</sup> ETH.MESH.06852118 at 2118-2129 (5/26/2000 Biocompatibility Review).

<sup>183</sup> ETH.MESH.06852120 (8/8/1997 Cytotoxicity Risk Assessment).

“there is some evidence to suggest that the PP [polypropylene] mesh from the sterile Ulmsten device may have cytotoxic potential.”<sup>184</sup> In addition, ISO Elution testing “resulted in marked cytotoxicity in tests conducted at Ethicon (Scotland).”

According to former Ethicon Medical Director, Dr. David Robinson, Ethicon never performed “a single long-term study . . . to determine whether or not the Ethicon mesh is clinically cytotoxic in women.”<sup>185</sup> In addition, in its IFUs and Patient Brochures, Ethicon never informed physicians or their patients about the possibility of cytotoxicity.<sup>186</sup> Dr. Robinson testified that if there is a clinical related outcome related to cytotoxicity, it is reasonable for physicians to want to know that the mesh in the TVT product had been tested multiple times to be severely or marked cytotoxic.<sup>187</sup>

Cytotoxicity can cause death to cells that can lead to an inflammatory response leading to a multitude of injuries, including serious adverse complications such as erosions, chronic pelvic pain, recurrence, worsening incontinence, dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction or the need for additional surgeries. Ethicon did not undertake any long term testing to determine whether the marked cytotoxicity found in the TVT mesh had long term consequences for permanent human use. This is true despite the fact that its own test results showed the mesh to be cytotoxic.

Because of the dangers and consequences that occur as a result of cytotoxicity, the fact that Ethicon had positive tests for cytotoxicity and did nothing to test for it makes the mesh in the TVT not suitable for permanent implantation. In addition, the potential for cytotoxicity or cell death is important information that physicians need to know in order to pass the

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<sup>184</sup> *Id.* and Robinson Dep. (9/11/13) 1098:23-1099:9.

<sup>185</sup> Robinson Dep. (9/11/13) 1101:24-1102:5.

<sup>186</sup> Robinson Dep. (9/11/13) 1114:15-18.

<sup>187</sup> Robinson Dep. (9/11/13) 1115:5-19.

information on to their patients so that an informed decision can be made about whether to have a permanent medical device implanted in their body. It is clear from Ethicon's Medical Director David Robinson that this information was never passed on to physicians despite the fact that it would have been reasonable for physicians to have this information. As a result, Ethicon did not act as a reasonably prudent medical device manufacturer in it failed to inform physicians and their patients about the risk of its mesh being cytotoxicity.

**F. Ethicon's warnings and disclosures of adverse events in its TVT Instructions for Use ("IFU") are inadequate based on the adverse reactions and risks associated with the TVT that have been known to Ethicon from the time the TVT was first sold and marketed**

The purpose of the IFU is for a medical device manufacturer to provide physicians with the information necessary for them to make decisions regarding the used a medical device for a particular patient. In addition, the IFU should disclose adverse reactions and risks known to the medical device manufacturer to the physician so that the risks can be relayed to the patient and an informed decision regarding the use of the product can be reached. Throughout my education, training, surgical and clinical practice, I have reviewed numerous IFUs for a variety of products, including mesh products in order to understand the proper way to use the device and to gain knowledge about the complications and adverse events associated with a device. I have extensive clinical experience with IFUs and instructing patients about the adverse events/risks contained in the IFU. Similar to Medical Directors, Dr. Martin Weisberg and Dr. David Robinson, I have gained expertise in IFUs through my extensive clinical experience reviewing IFUs, and consenting patients regarding IFUs, including Ethicon's own pelvic mesh products including the TVT line and Prolift.

Catherine Beath, Ethicon's former Vice President of Quality Assurance and Regulatory

Affairs, testified that “physicians should be made aware of all the significant safety risks associated with the product in the IFU.”<sup>188</sup> And, “a reasonably prudent medical device company would continually update the label consistent with developing data and information that becomes known to the company” when it is appropriate.<sup>189</sup> Similarly, former Medical Director Dr. David Robinson testified that the warnings and adverse event section of the IFU should include all significant risks and complications related to the procedure and the mesh.<sup>190</sup> According to Dr. Robinson, a device manufacturer must include this information because you want to make sure the doctors have all the information they need to adequately inform patients who are deciding to use the product.<sup>191</sup> According to Ethicon Medical Director Dr. Martin Weisberg, the goal of the IFU is to communicate the most important safety risks attributable to the TVT device and that an IFU should never exclude known hazards or complications.<sup>192</sup>

Dr. Weisberg also believes that an IFU should not knowingly underestimate the risks of using the product.<sup>193</sup> And, if an IFU excludes known complications or understates the risks, it “fails in one of its principal purposes.”<sup>194</sup> Finally, Peter Cecchini, a 43 year Ethicon employee and Regulatory Fellow and the person responsible for the TVT 510K, testified that the “regulatory standard for the IFU is the known risks are supposed to be included in the adverse reactions.”<sup>195</sup> Mr. Cecchini testified that he relies on medical affairs to make sure he knows the known risks so they can be included in the IFU.<sup>196</sup>

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<sup>188</sup> Beath Dep. (7/12/13) 592:7-11.

<sup>189</sup> Beath Dep. (7/11/13) 198: 8-13.

<sup>190</sup> Robinson Dep. (9/11/13) 238:12-25.

<sup>191</sup> Robinson Dep. (9/11/13) 239:1-11.

<sup>192</sup> Weisberg Dep. (8/9/13) 659:19-660:15.

<sup>193</sup> *Id.* at 960:13-16.

<sup>194</sup> *Id.* at 961:10-17.

<sup>195</sup> Cecchini, 10/22/12, 65:5-12.

<sup>196</sup> Cecchini, 10/22/12, 65:18-24.

**1. The TVT IFU Did Not Include All Known Risks, Was Inaccurate and Was Not Updated.**

**a. The IFU did not include all known risks.**

As noted above, Ethicon did not include the proper information concerning the dissection in the original IFU. There were also numerous other potential risks that were not included in the IFU at launch.

If you compare the adverse reactions/risks in the TVT IFUs to the adverse reactions/risks that were available and known to Ethicon at the time of the launch of TVT, it is clear that there are numerous adverse events absent from the IFU. From the time TVT was launched in the United States in December of 1998 to the present day, there have been ten versions of the Ethicon TVT IFU. These include the following versions: October, 1998, April, 1999, May 1999, September 8, 2000, December 22, 2003, February 11, 2005, April 7, 2006, October 13, 2008, November 29, 2010, and May, 2015. A chart showing the Adverse Reactions/Risks section for each version of the TVT Instructions for Use is set forth below.

Product	Production Prefix	Start Bates	End Bates	First Use Date	Last Use Date	Adverse Reactions / Risks
TVT	ETH.MESH	00203477	00203482	10/27/98 (U.S Launch IFU)	04/11/99	<p>*Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation</p> <p>*As with all foreign bodies, PROLENE mesh may potentiate and existing infection. The Plastic sheath initially covering the PROLENE mesh is designed to minimize the risk of contamination</p> <p>*Over correction i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction</p>
TVT	ETH.MESH	00204514	00204519	04/11/99	05/18/99	Same as 10/27/1998 IFU

TVT	ETH.MES H	0020456 2	002045 93	05/18/99	09/08/00	<p>* Punctures or lacerations of vessels, nerves, bladder or bowel may occur during needle passage and may require surgical repair.</p> <p>* Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation.</p> <p>* As with all foreign bodies, PROLENE Mesh may potentiate an existing infection. The plastic sheath initially covering the PROLENE Mesh is designed to minimize the risk of contamination.</p> <p>* Over correction, i.e., too much tension applied to the tape may cause temporary or permanent lower urinary tract obstruction.</p>
TVT	ETH.MES H.	5225354	522538 5	09/08/00	11/26/03	Same as 05/18/1999 IFU
TVT	ETH.MES H.	2340306	234036 9	12/22/03	02/11/05	Same as 05/18/1999 IFU

TVT	ETH.MES H.	2340471	234050 3	02/11/05	04/07/06	Same as 05/18/1999 IFU
TVT	ETH.MES H.	5222673	522270 4	4/07/06	10/07/08	Same as 05/18/1999 IFU
TVT	ETH.MES H.	2340504	234056 7	10/13/08	11/22/10	Same as 05/18/1999 IFU
TVT	ETH.MES H.	3427878	342794 5	11/29/10	May, 2015	Same as 05/18/1999 IFU.
TVT	N/A	N/A	N/A	May, 2015	To Present Day	<p>*Punctures or lacerations of vessels, nerves, structures or organs, including the bladder, urethra, or bowel, may occur and may require surgical repair.</p> <p>*Transitory local irritation at the wound site may occur.</p> <p>*As with any implant, a foreign body response may occur. This response could result in</p>



					<p>extrusion, erosion, exposure, fistula formation and/or inflammation.</p> <p>*Mesh extrusion, exposure, or erosion into the vagina or other structures or organs.</p> <p>*As with all surgical procedures, there is a risk of infection. As with all foreign bodies, PROLENE mesh may potentiate an existing infection.</p> <p>*Over correction, i.e., too much tension applied to the tape may cause temporary or permanent lower urinary tract obstruction.</p> <p>*Acute and/or chronic pain.</p> <p>*Voiding dysfunction.</p> <p>*Pain with intercourse which in some patients may not resolve.</p> <p>*Neuromuscular problems, including acute and/or chronic pain the groin, thigh, leg, pelvic and/or abdominal area may occur.</p> <p>*Recurrence of incontinence.</p> <p>*Bleeding including hemorrhage, or hematoma.</p> <p>*One or more revision surgeries may be necessary to treat these adverse reactions.</p> <p>*PROLENE mesh is a permanent implant that integrates into tissue, In cases in which the PROLENE mesh needs to be removed in part or whole, significant dissection may be required.</p> <p>*Seroma</p> <p>*Urge incontinence</p> <p>*Urinary frequency</p>
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						*Urinary Retention *Adhesion formation *Atypical vaginal discharge *Exposed mesh may cause pain or discomfort to the patient's partner during intercourse. *Death
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In all six versions of the TVT IFU from May 19, 1999 to May of 2015, the Adverse Reactions/Risks section has remained exactly the same. It reads as follows:

#### ADVERSE REACTIONS

- \* Punctures or lacerations of vessels, nerves, bladder or bowel may occur during needle passage and may require surgical repair.
- \* Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation.
- \* As with all foreign bodies, PROLENE Mesh may potentiate an existing infection. The plastic sheath initially covering the PROLENE Mesh is designed to minimize the risk of contamination.
- \* Over correction, i.e., too much tension applied to the tape may cause temporary or permanent lower urinary tract obstruction.<sup>197</sup>

Despite only listing the above adverse reactions/risks, it is clear from the testimony of Senior Ethicon Employees in both the Medical Affairs and Regulatory Affairs that every adverse reaction/risk that Ethicon has scientific knowledge of today, it had scientific knowledge about at the time the TVT was first sold in and certainly in 2004 when the first TVT was sold, marketed and launched. Medical Director, Piet Hinoul testified that Ethicon understood the following adverse events occurred from the time the TVT was first sold, years before the first TVT was sold:

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<sup>197</sup> ETH.MESH.02340406.

Erosions through vaginal epithelium Infection  
 Pain  
 Urinary Problems  
 Erosions that could decrease patient's quality of life  
 Dyspareunia  
 Need for additional surgeries  
 Need for the removal of device  
 Urinary Tract Infections  
 Dysuria  
 DeNovo Urgency  
 Mesh Exposure  
 Fistula Formation  
 Hematoma  
 Abscess Formation  
 Narrowing of vaginal wall  
 Erosion which can occur any time in future  
 Contracture of mesh causing pain  
 Complications making it impossible to have sexual relations  
 Worsening Incontinence

Yet, none of these were in the TVT IFU at launch. There have been two significant updates to the Adverse events section of the TVT IFU since launch, one in May of 1999, and one in May of 2015. The May, 1999 updates to the IFU, including the addition to the Adverse Reactions section, were part of a corrective action plan taken by Ethicon due to a number of Serious Adverse Events being reported with the TVT device, 25 of which came to light in the two months prior to the IFU update. The majority of these Adverse events involved injury to vessels, bladder or bowel.<sup>198</sup> The Adverse Events section of the IFU was updated in May of 1999 to include the following:

- Punctures of lacerations of vessels, nerves, bladder, or bowel may occur during needle passage and may require surgical repair.**

In addition to the updates to the Adverse Reactions section of the IFU, the Warnings and precautions section was updated to include the following statements:

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<sup>198</sup> ETH.MESH.07424335.

- The TVT procedure should be performed with care to avoid large vessels, nerves, bladder and bowel. Attention to local anatomy and proper passage of needles will minimize risks.
- Retropubic bleeding may occur postoperatively. Observe for symptoms or signs before releasing patient from hospital.

The May, 2015 IFU included a large number of significant updates, including warnings about pain, chronic pain, dyspareunia for the patient and/or her partner, need for multiple surgeries, and the difficulty in removing all or part of the device. These adverse events, which were added to the TVT IFU in May of 1999 and May of 2015, are all risks that Ethicon knew of at the time of launch of the TVT, and should have been included in the IFU since launch.

In addition, as discussed more fully throughout this report, Ethicon failed to include significant risks in its IFU related to the Prolene polypropylene mesh, including potential cytotoxicity, association with tumor formations and that the mesh can degrade, shrink and contract. The IFU also fails to include risks associated with the Prolene mesh, including chronic foreign body reaction, fibrotic bridging, infections/biofilms, fraying/particle loss and roping/curling of the mesh. Moreover, the IFU fails to inform physicians that patients may require multiple surgeries to treat erosions, that erosions could be severe and untreatable, that patients could endure lifelong severe pain or dyspareunia/painful sex, removing the mesh and revision surgeries can be complicated and challenging for both the patient and physician, and complete removal of the TVT mesh is likely impossible.

Medical Director Dr. Weisberg testified that Ethicon did not include: “permanent, lifelong, worsening and debilitating pain”, lifelong risk of surgical repairs for erosions, “severe or chronic inflammation“, collapse under strain and cause fibrotic bridging, that the product can degrade, that polypropylene is cytotoxic, severe erosion, or particle loss.<sup>199</sup>

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<sup>199</sup> Weisberg Dep. (8/9/13) 968:12-972:21.

But Ethicon did not disclose this information to physicians in its IFUs regarding characteristics of the old construction mesh in TVT, including that it is small pore, heavy weight mesh, it degrades over time, causes chronic foreign body reactions, fibrotic bridging, mesh contracture/shrinkage, fraying, particle loss, roping and curling of the mesh, and that it deforms and the pores collapse with tension. In fact, Ethicon medical director Piet Hinoul testified if Ethicon did warn that roping, curling and particle loss can cause pain and erosions Ethicon would have to take the mesh off the market.<sup>200</sup>

Moreover, the IFU failed to inform physicians of the frequency, duration and severity of the risks associated with the TVT device until the May, 2015 IFU update. In addition, former Medical Director, Dr. David Robinson, testified that Ethicon never informed physicians that patients may require multiple surgeries to treat erosions, that erosions could be severe and untreatable, and that patients could endure lifelong severe pain or dyspareunia/painful sex. This is true despite, as discussed above, Ethicon had scientific knowledge of the risks at the time of launch.

**b. The IFU inaccurately portrayed risks.**

In addition to excluding certain known risks, Ethicon significantly downplayed the risks that it actually listed in its IFU. This is especially true with respect to erosions. On the topic of erosions, in the Adverse Event/Risks section in the TVT IFU, in place from the time of launch until present day, it states:

Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation.

This language significantly downplays the permanent nature of erosions and suggests to

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<sup>200</sup> Trial testimony of Piet Hinoul, *Batiste v. Ethicon*, page 67.

physicians that erosions are a “transitory” or temporary problem. As shown in an email exchange between Ethicon’s Associate Medical Director of Worldwide Customer Quality Meng Chen, M.D., Ph.D and Bryan Lisa in the Regulatory Affairs Department, it was clear that the adverse events were not “transitory.” Chen wrote, “Pardon me again, from what I see each day, these patient experiences are not “transitory” at all.”<sup>201</sup>

Ethicon also had scientific evidence that erosions could occur many years after implantation of the device. In Minutes from June 22, 2001 Scientific Advisory Committee on Pelvic Floor Repair, it was a “Consensus: Erosion is a risk. Erosion, possibly an infection response. Typically seen by 3 mos, usually by 6-12 mos. Can present late, 3 years. To vagina- not a good situation. To bladder, urethra or rectum-a very bad situation.”<sup>202</sup> “There have been reports of erosions into the urethra that are not picked up until months even years after the procedure.”<sup>203</sup> In October 2002, Medical Director Dr. Martin Weisberg was involved in email exchange with European Science Director Axel Arnaud about downplaying risks with respect to erosions. Specifically, Dr. Arnaud suggested to Dr. Weisberg that Ethicon needed “to be more elusive” when discussing potential complications like erosions.<sup>204</sup>

According to Medical Director Dr. Martin Weisberg and former Medical Director Dr. David Robinson, Ethicon never disclosed or warned doctors or patients in IFUs or Patient Brochures that the use of TVT slings can cause lifelong risk of erosions.<sup>205</sup> Despite the fact Ethicon had scientific feedback from one of its own doctors that experiences were not transitory and that she had concerns about the IFU and the transitory language, Ethicon never informed physicians or disclosed it in its IFU.

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<sup>201</sup> ETH.MESH.04093125 (1/29/09 Email between Meng Chen and Bryan Lisa).

<sup>202</sup> ETH.MESH.02089392.

<sup>203</sup> ETH.MESH.04099233 (September 24, 2008 email from Melissa Day to Meng Chen and others).

<sup>204</sup> ETH.MESH.03910175-03910177.

**c. Ethicon failed to update the IFU.**

Once TVT was on the market, Ethicon refused to appropriately update the IFU to reflect the known risks above and additional risks. On December 19, 2008, after Dr. Meng Chen had received a complaint from a number of patients about not being fully informed of the risks of the procedure, she recommended to senior management that the IFU be updated:

[The patient] was given the most accurate consent for the potential adverse reaction known in 2005. However, we are in 2008 now, and there are two more TVT family products (TVTO and TVTS) on the market. Our post-market knowledge with these products are much more than what we have in the IFUs of all three types of TVTs (TVT-Abdominal, Obturator and Secur). My reason for bringing this point to you is maybe you may look into it from senior management perspective and to facilitate the IFU update for all three TVTs, particularly in the area of 'Potential Adverse Reactions'.... One of the paths for a better pre-operative consent is to provide an updated IFU to the operating physicians that reflecting the current knowledge of the manufacturer's on the potential adverse reactions."<sup>206</sup>

In a January 29, 2009 email, Meng Chen wrote again that the IFU should be updated to make it clear that the irritation and foreign body response were a result of the tape itself and that this "could result in tape extrusion, tape erosion, fistula formation or inflammation."<sup>207</sup> When working on the Mini-O/Abbrevio IFU, Ethicon employees noted that the older IFU's should be updated. Dr. Aaron Kirkemo wrote:

I would agree from the meeting today that now that we have 12+ years of experience with TVT classic that learnings from the field would probably drive a relook at the TVT Classic IFU as reflected by some of your comments in this document."<sup>208</sup>

In response, Dr. Robison asked: "has there been agreement re: a project to revise TVT and TVTO?"<sup>209</sup> There was indeed agreement at upper management – there would be no revision to

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<sup>205</sup> Weisberg dep. (8/9/13) 968:2-969:10; Robinson Dep. (9/11/13) 329:12-330:7.

<sup>206</sup> ETH.MESH.04092868.

<sup>207</sup> ETH.MESH.04094863 (e-mail from Dr. Meng Chen to Bryan Lisa, Jan. 29, 2009).

<sup>208</sup> ETH.MESH.01239065 at 9066 (July 14, 2009 email from Aaron Kirkemo MD to Piet Hinoul MD and David Robinson MD).

<sup>209</sup> *Id.*

incorporate what they had learned: “Per Scott C and Stale, they just want to “look forward” with this project. Their plans are to leave TVT Classic [and TVT] as is. Aaron.”<sup>210</sup>

Interestingly, in 2008, 2011, 2012, and 2015 Ethicon added numerous adverse reactions and risks to its Patient Brochures that have never been disclosed in previous versions of the Patient Brochures. Some of these adverse reactions and risk have never been disclosed in the TVT IFUs even at present time, and all of these were not in TVT IFUs prior to May, 2015. These risks are as follows:

**From Patient Brochures (never in IFU prior to May, 2015. Those in Yellow are still not in IFU)**

2008

Difficulty urinating Pain

**Scarring**

Mesh Exposure requiring treatment

2011

Mesh exposure into the vaginal canal

Mesh exposure associated with pain during intercourse for the patient and partner

Mesh exposure which may require removal of exposed mesh in office or operating room

2012

Pelvic Pain

Development of Urinary Incontinence

Voiding Difficulties

Hemorrhage or hematoma

Urinary tract infection Wound healing problems Injury to ureters

Pelvic abscess formation

Risk of infection

**Vaginal scarring**

**Mesh contracture (mesh shortening due to scar tissue)**

2015

**Anesthesia risks**

Pain (temporary or chronic)

Seroma

Neuro-muscular problems (including pain in the groin, thigh, leg, pelvic or abdominal area)

Adhesion formation

**Abnormal vaginal discharge**

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<sup>210</sup> *Id.*



Recurrent incontinence

Death

These complications may require additional medical treatment, hospitalization, or surgery

These complications may resolve over time or may be chronic

There is also a risk that the mesh material may erode into another organ such as the bladder or urethra (mesh erosion) and cause pain and additional problems.

Mesh erosion would likely require additional surgery to remove the mesh from the organ.

Some of these risks have been disclosed in Ethicon's other PROLENE mesh IFUs. For example, Ethicon's IFU for PROLENE hernia mesh states as follows: "The use of PROLENE Mesh in contaminated wounds should be with the understanding that subsequent infection may require removal of the material."<sup>211</sup> Even though Ethicon changed its Patient Brochures in 2011 and 2012 to include additional significant adverse events/risks, it never added the same information to the TVT IFU until May of 2015. This is true despite the fact that Ethicon had internal discussions about updating the IFU in 2009 after the 2008 FDA Public Health Notification (PHN). Specifically, a meeting was held to decide, among other issues, whether to update "the current Adverse Reaction of tape exposure and post-operative dyspareunia in the TVT-family products...."<sup>212</sup>

After discussing the 2008 PHN, competitors' labels and Remetrex issues, impressions were that tape exposure/erosion/extrusion were very frequently reported, patients did not feel there were adequate pre-op consent or risk-benefit assessment, patient specific concerns about exposure/erosion/extrusion, incontinence recurrence, post-operative dyspareunia and pain-affect quality of live and affect daily routine, re-operations and post-operative complications disproportionate to pre-operative-consent-expectations.<sup>213</sup> Despite these discussions and Ethicon's scientific knowledge of these serious, devastating and life-changing adverse

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<sup>211</sup> ETH.MESH.02342102.

<sup>212</sup> ETH.MESH 04081189.

events/risks, to this day, it has never updated or changed its IFU to include this information.

Repeatedly, the reason given for not updating an IFU to make it more accurate and safer was that doing so would threaten the launch timing of a new product. For example, when discussing the IFU for TVT-Exact, Dr. David Robinson cautioned against making too many changes from the original TVT-R IFU: “Just to clarify... the more changes we make to the IFU that differ from TVT-Classic, the higher the risk will be to the submission timing.”<sup>214</sup>

In summary, Ethicon did not fully inform physicians about numerous adverse reactions/risks associated with the TVT despite the fact that Ethicon had scientific knowledge of the risks from the time the product was first sold. As a result, physicians were unable to fully consent and inform patients of the risk associated with TVT. In addition, some risks included by Ethicon in the IFU are mischaracterized to minimize the actual risk. Finally, when given numerous opportunities to update the IFU, and in the face of specific requests to do so from numerous medical professionals, Ethicon did not make the necessary updates. To a reasonable degree of medical certainty, this prevented physicians and patients the ability to make an informed choice regarding the use of the TVT. For a surgeon to properly inform the patient of all the known risks involved in any procedure involving an implantable medical device, the surgeon relies upon the manufacturer to have scientific knowledge of and convey all characteristics of its products that could impact safety and efficacy. Specifically, surgeons rely on the “Adverse Events/Risks” section of a medical device IFU to gain scientific knowledge regarding adverse events or undesirable effects that the company knows are associated with the product.

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<sup>213</sup> *Id.*

<sup>214</sup> ETH.MESH.10632650 at 10632652.

**D. The TVT Device Is Not Designed for Special Patient Populations Nor Does the IFU or Marketing Inform Physicians or These Patients of Poorer Outcomes or Higher Risks.**

Ethicon promoted the TVT as a “reproducible” technique that was appropriate for all patients. For example, Ethicon instructed its sales force to specifically target physicians to use the TVT and TVT in obese patients.<sup>215</sup> However, as Ethicon’s Medical Director, Dr. Kirkemo, testified obese patients do not fare well with these devices.

Q. One of the things that was actually shown in the TVT World study that you worked on was that for obese patients, for example, the efficacy was significantly down when slings were used in obese patients; is that correct?

A. Obese people tend -- not to do as well.

In fact, Ethicon’s study showed obese patients had about one half the success of those patients who were not obese. In addition, as Dr. Kirkemo testified, obese women suffered from more complications: “Their chance of success goes down. Their risk of complications goes up.”<sup>216</sup>

Yet, Ethicon did not put this critical information into the IFU. Dr. Kirkemo testified:

Q. Did you ever put that in the IFU?

A. No....<sup>217</sup>

Not only did Ethicon not put this critical information in the IFU, Ethicon also did not inform patients:

Q. Did you ever tell patients that in a single patient brochure, that if they were obese, their chances of this being successful were less than half?

A. We did not.<sup>218</sup>

Ethicon also did not include information in its IFU about how the TVT had less efficacy and higher risk for older women or younger, active women.

Q. Did you -- you also learned in the TVT World study, or maybe you knew

<sup>215</sup> See, e.g., ETH.MESH.00640394 (trying to convince physicians to use TVT on obese patients); ETH.MESH.05119622 at 9623 (TVT “is a good choice for the obese patient or elderly patient....”).

<sup>216</sup> Kirkemo Dep. (1/7/2014) 556:24-557:1.

<sup>217</sup> Kirkemo Dep. (1/7/2014) 556:4-19.

<sup>218</sup> Kirkemo Dep. (1/7/2014) 557:5-557:9.

- this before, too, that being elderly decreased, or being very young, in fact, decreased the efficacy of the Ethicon sling procedures; correct?
- A. With any incontinence operation, old people tend not to, you know, do as well.
- Q. And was that ever put in a patient brochure or communicated to patients as far as you know?
- A. As near as I can tell, in any marketing document, no.
- Q. And what about the very young or the younger women; that was shown in TVT World that even younger women had lower efficacy; correct?
- A. Some women that are very, very active can -- and have ISD can overcome the effect of the sling.
- Q. In other words, the sling can fail.
- A. The sling can be less than a hundred percent effective.
- Q. And that was never actually communicated to patients as far as you know, correct, by Ethicon?
- A. To my knowledge, no.
- Q. And neither the older women or the younger women in issue we were just talking about, neither of those are included in the IFU; correct?
- A. Those specific things are not mentioned.<sup>219</sup>

Ethicon also did not inform physicians and patients that the TVT devices, including the TVT would not work as well and would be more dangerous for women who smoked or who had Diabetes – a very large percentage of the patients to whom TVT was being marketed:

- Q. Smoking decreases the efficacy of slings; correct?
- A. Yes.
- Q. Diabetes decreases the efficacy of slings; correct?
- A. It can because you have neurologic, you know, disease.
- Q. Neither smoking nor diabetes is listed as a potential contraindication or something special to look for in the IFU; correct?
- A. It is not listed in the IFU....
- Q. And Ethicon never communicated to patients that smoking would increase their risk of adverse outcomes or decrease the chance that the sling would work; correct?
- A. We did not.
- Q. And the same with diabetes. Ethicon never communicated to patients when they were selling TVT devices that diabetes would decrease the chance that the device would work or increase the chance that they would have an adverse event; correct?
- A. I did not see that, no.

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<sup>219</sup> Kirkemo Dep. (1/7/2014) 557:10-558:21.

Ethicon knew that there were other patient populations that also faced increased risk or lower success rates with the TVT. Specifically, Ethicon knew that women who had prior pelvic surgery, prior pelvic injury or an infection, could be at increased risk if undergoing the TVT surgery. In 1999, Ethicon discussed putting another warning in the TVT IFU related to patients who had previous surgeries because of scar tissue.<sup>220</sup> The proposed warning was “patients who have had previous surgical procedures may require special consideration due to scar tissue.”<sup>221</sup> Ethicon was concerned that the risk of mesh extrusion was increased in women with postoperative infection, previous vaginal surgery, vaginal atrophy or vaginal injury.<sup>222</sup> Dr. Isenberg, Ethicon medical director, admitted that if Ethicon knew this, it would have been reasonable to include a warning and, further, physicians and their patients would want to know this information. However, Ethicon was “under extreme pressure” to finish the IFU to meet a scheduled launch date in 1999, so did not include the statement in the April, 1999 IFU update.<sup>223</sup> Ethicon planned to discuss the issue for possible inclusion in the IFU in the future, but I have seen no evidence of such discussion, and this warning never made it into the IFU. Again, despite these discussions in 1999 and former Medical Director Dr. Isenberg’s opinions that it would be reasonable to have this information in the IFU, to this day, this critical information remains absent from the IFU.

Finally, Ethicon also knew that the method of anesthesia utilized during the TVT surgery could affect patients’ outcomes, but didn’t disclose that information to physicians or patients. Ethicon’s internal documents, including interviews with Ethicon’s key opinion leader, Dr. Carl Nilsson, Ethicon U.S. Marketing Research documents, and letters from the inventor of the TVT

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<sup>220</sup> ETH.MESH.08505071, ETH.MESH.00203456, Eth.Mesh.00159634-00159719 at 00159697.

<sup>221</sup> ETH.MESH.08505291.

<sup>222</sup> Id.

<sup>223</sup> ETH.MESH.00203456.

(Dr. Ulmsten) show that Ethicon knew that performing the TVT procedure under general anesthesia as opposed to local anesthesia decreased the chance for success of the surgery and also increased a patient's risk of urinary retention and erosions.<sup>224</sup> This is further supported by the testimony of Dr. Richard Isenberg, a former medical director for Ethicon, who was at Ethicon just after the initial launch of the TVT.<sup>225</sup> Dr. Isenberg testified that the IFU could be better worded so that physicians knew that local anesthesia should be preferred over general anesthesia.<sup>226</sup> In addition, according to Dr. Isenberg, Dr. Ulmsten, inventor of the product, informed Ethicon that the TVT procedure should be carried out under local anesthesia unless it was a special situation.<sup>227</sup> Despite the inventor's desire to have this language listed, to this day, it does not appear in the IFU.<sup>228</sup> Dr. Isenberg was also aware that using general anesthesia could cause the success rate of the procedure to go down and put the patient at increased risk for urinary retention and erosions.<sup>229</sup> He testified that he believes a responsible company should have put this information in the IFU because the IFU is the one document that you can count on every physician receiving.<sup>230</sup> I agree. Again, however, to this day, this warning does not appear in the TVT IFU.

The TVT is dangerous and can cause significant, lifelong injury to women, due in part to its "one-size fits all" design. Ethicon failed to inform physicians that there are certain patient populations that face greater risks and less success with the TVT. Ethicon needed to pass this critical information on to physicians in the IFU so that they could have an appropriate informed consent discussion with their patients.

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<sup>224</sup> Eth.Mesh.04048515-04048520; Eth.Mesh.00130934-00130941, Eth.Mesh. 00400954-00400956.

<sup>225</sup> Isenberg, 11/6/13, 461:16-530:13.

<sup>226</sup> Id. at 526:25-528-18.

<sup>227</sup> Id. at 553:15-554:21.

<sup>228</sup> Id.

<sup>229</sup> Id. at 566:9-15.

<sup>230</sup> Id. at 566:3-8.

Accordingly, it is my opinion to a reasonable degree of medical certainty that the TVT as designed is not effective for special patient populations. In addition, the TVT is dangerous and can cause significant, lifelong injury due in part to its “one-size fits all” design. Moreover, Ethicon failed to inform physicians of the importance of these patient variations and the potential for permanent, serious injury from the TVT. Because Ethicon failed to inform physicians, Ethicon also removed the ability of the physicians to fully inform patients of these risks.

**E. Ethicon failed to reveal material facts about complications and conflict of interests regarding data promoted in the materials.**

Since the TVT was first launched, Ethicon has sent materials in various forms to physicians promoting long term follow up data on the original cohort of patients implanted with the TVT from 1995-1996.<sup>231</sup> Ethicon continued to cite to this data in its TVT materials.<sup>232</sup> In addition, the materials tout low complication rates related to various adverse reactions, including erosions. These materials include press releases, marketing brochures and email blasts.

The long term data primarily relied on by Ethicon throughout these materials relates to the Ulmsten/Nillson studies. These studies were originally started by Dr. Ulmsten, the inventor of the TVT, and continued by Dr. Nillson after Dr. Ulmsten’s death. Prior to selling the TVT to Johnson & Johnson, Dr. Ulmsten owned a company called Medscand. As discussed more fully below, Johnson & Johnson hired Dr. Ulmsten and Medscand to conduct studies related to the TVT. To this day, Ethicon relies heavily on these studies and uses them in numerous promotional materials despite the fact that Ethicon never disclosed to physicians the potential

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<sup>231</sup> ETH.MESH.0015598, ETH.MESH.00658058, ETH.MESH.01186068, ETH.MESH.02236784, ETH.MESH.02237103, ETH.MESH.03459211, ETH.MESH.05183409, ETH.MESH.00339437; ETH.MESH.05794787.

conflict of interest and inherent bias that exists due to Dr. Ulmsten's relationship with Ethicon and Johnson & Johnson. In addition, Ethicon never disclosed to physicians that the device used in the original Medscand study was different than the TVT device. It is important to physicians using the TVT that the data in these types of promotional materials is accurate, unbiased and that physicians are informed about any potential conflicts of interest in the data contained within the materials. In other words, physicians rely on Ethicon to provide fair and balanced information and to ensure that physician have been given all the data and not just the positive press release data.

Despite using the Ulmsten data to promote the TVT, Ethicon never disclosed to physicians the bias and inherent conflict of interest related to the Ulmsten data. Specifically, in its promotional materials, Ethicon (Johnson and Johnson) never informed physicians about its relationship and contracts with Professor Ulmsten and his company Medscand. It is clear from the contracts that the publications and data from Dr. Ulmsten were contracted for hire by Johnson and Johnson International.<sup>233</sup>

The License and Supply Agreement between Johnson and Johnson International and Medscand (Ulmsten's Company) dated February 13, 1997, states in section 3.6 Milestone Payments:

Johnson and Johnson International (JJI) shall pay shall pay to Medscand the following payments (b). A payment in the amount of \$400,000.00 due on February 28, 1997; provided, however, that in the event that Clinical Trials as specified in Exhibit C have not been completed by such date, then such amount shall not be due until the completion of the Clinical Trials.<sup>234</sup>

Under Exhibit F, Consulting Agreement with Professor Alf Ivar Ulmsten, section 4 Confidential Information Rights to Inventions and Copyrights (B) it states:

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<sup>232</sup> ETH.MESH.00163582.

<sup>233</sup> ETH.MESH.08696085 at 085-6134.



Any copyrightable work whether published or unpublished created by supplier Dr. Ulmsten directly as a result of or during the performance of services herein shall be considered a work made for hire, to the fullest extent permitted by law and all rights, titles and interest herein, including worldwide copyrights shall be the property of the company as the employer and party specially commissioned said work.<sup>235</sup>

Finally, in Exhibit C, Clinical Trials, it states:

The results of clinical trials will be considered acceptable if, first, they do not differ significantly from the results published in the original article published in the Int. Urogynecol J 1996-7:81-86 by U. Ulmsten, et.al., with regards to the following items: Safety 1.1, preoperative complications 1.2 , post operative complications 1 year from operation 2. Efficacy. Second Long term results over 1 year from operation do not show a deterioration of rates significantly different from those of the standard suburethral slingplasties. It is assumed that from 12 – 60 months a gradual decrease in efficacy of 5% is normal. 3. No significant numbers of unexpected i.e. not addressed in the original article published in the Int. Urogynecol J 19967 81-86 by U.Ulmsten at et.al. procedure related i.e. not addressed in the review article published in the Int. Urogynecol J 19945: 228-239 by G. N. Ghomiem et.al. complications appear at any time in the postoperative course.<sup>236</sup>

In total, Dr. Ulmsten stood to gain millions of dollars for the 6 papers that he published on the TVT device. In addition, the results of those studies would be found acceptable for payment only if they did not differ from the parameters sent by Johnson & Johnson regarding complications and efficacy. The Ulmsten studies have an inherent conflict of interest and bias as they were “made for hire” and standards were set by Johnson & Johnson. As set forth above, if Dr. Ulmsten did not meet the standards set forth by Johnson & Johnson, he did not receive substantial payments for the “studies.” As a result of this relationship, there is a clear conflict of interest and potential for enormous bias issues.

The conflict of interest and bias created by the relationship between Ethicon and Dr. Ulmsten was acknowledged by Dr. Axel Arnaud, Ethicon’s European Medical Director, in a

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<sup>234</sup> ETH.MESH.08696091.

<sup>235</sup> ETH.MESH.0869116.

<sup>236</sup> ETH.MESH.08696132.

recent deposition. Specifically, Dr. Arnaud testified that such an agreement like the one discussed above between Dr. Ulmsten and Johnson & Johnson creates a potential conflict of interest.<sup>237</sup> Dr. Arnaud also acknowledged that when Johnson & Johnson enters into this type of agreement with a physician or his company and the study is published, there “certainly” needs to be a disclosure of the relationship.<sup>238</sup> Additionally, Former Ethicon Medical Director, Dr. David Robinson, testified that in his experience working in the industry for medical device manufacturers, it is best that potential biases be disclosed.<sup>239</sup> He also testified that if publications from somebody like Ulmsten or Nilsson about safety and efficacy are being published, it is best if they disclose that they have a financial bias or conflict of interest.<sup>240</sup> In fact, in an April 2009 email exchange with Medical Director Piet Hinoul about a physician who, like Ulmsten, is a consultant and inventor for competitor Boston Scientific, Dr. Robinson states that that situation presents “enormous bias issues.”<sup>241</sup> Despite two of its medical directors testifying that the relationship between Ulmsten and carried over to Nilsson presents a conflict of interest and bias, Ethicon has never disclosed this information in its promotional pieces. This is information physicians and patients have a right to know so that a proper informed decision regarding the value of the data in the studies and the use of the product can be made.

Aside from never disclosing to physicians the underlying conflict of interest and bias of the Ulmsten studies in its promotional pieces, Ethicon also never informed them about other problems with the data, including incomplete data on the original cohort, data incorrectly reported and erosion rates underreported. In the original 510k submission for TVT Classic,

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<sup>237</sup> Arnaud Dep. (7/20/13) 497:24-501:21, 509:8-17.

<sup>238</sup> Arnaud Dep. (7/20/13) 514:17-515:1.

<sup>239</sup> Robinson Dep. (9/11/13) 214:15-21.

<sup>240</sup> Robinson Dep. (9/11/12) 215:8-13.

Ethicon used Medscand data from the Scandinavian Multicenter Study.<sup>242</sup> The report shows that 12 month follow was obtained for 90 of the original 131 patients, without explanation of why there was a loss of 41 patients from the study. The study also describes a complication of wound infection: “while the vaginal infection required surgical intervention with resection of exposed mesh.” This represents a vaginal mesh erosion/extrusion/ exposure and needs to be reported as such. However, when the paper was published (Ulmsten, Int Urogynecol J 1998), the paper states that there was no defect healing and no tape rejections. It further misrepresents the outcome for this patient as “The patient with the wound infection had vaginal atrophy. After minimal vaginal wall resection and effective local estrogen treatment she healed without further intervention. There was no tape rejection.”

If Ulmsten had reported a mesh erosion/extrusion/exposure with mesh excision in his study, it would not have been acceptable under Exhibit C of his consulting contract for payment of the \$400,000.<sup>243</sup> This demonstrates that the results of this paper were potentially biased by the payment Ulmsten would receive for favorable data and should discount the data. At the very least, Ethicon should have informed physicians about the relationship between Ethicon and the Ulmsten studies.

Many of the marketing brochures tout the “[t]he urethral erosion rate less than or equal to that of traditional slings; no reported urethral erosions in 10 studies of 50+ patients.”<sup>244</sup> The reference used for the first part of this statement is from Dr. Gary Leach ) who looked at traditional sling procedures done before 1993, when traditional slings were performed at the bladder neck and purposely placed under tension to treat severe stress urinary incontinence

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<sup>241</sup> ETH.MESH.03259439; Robinson Dep. (9/11/13) 219:6-220:10.

<sup>242</sup> ETH.MESH 00371587.

<sup>243</sup> ETH.MESH 08696132.

<sup>244</sup> ETH.MESH 00339439.

from intrinsic sphincter deficiency (particularly among Urogynecologists).

The second part of this statement regarding “no urethral erosions” is incorrect. In published studies, Dr. Karram found one case of urethral erosion in his study of 350 Gynecare TVTs performed (Karram Obstet Gynecol 2003) and Hammad found nine cases of urethral erosion in his study (Hammad Eur Urol 2005).<sup>245</sup> His study followed the complications of 1459 patients 993 of whom had Gynecare TVT, while the remainder has SPARC procedures. While the authors do not break down the incidence of urethral erosion by product, it is exceedingly unlikely that all erosions happen in the SPARC group.

The statement regarding “no urethral erosions” also did not include deTayrac's 2003 paper of 61 patients (31 TVTs) which showed a 3% urethral erosion rate.<sup>246</sup> Dr. Shlomo Raz described a study of 26 patients who presented with voiding dysfunction, including symptoms of severe urethral, pelvic and genital pain, urinary retention, recurrent UTIs, de-novo urgency with urge incontinence found to have mesh from a sling procedure in the bladder or urethra.<sup>247</sup> Their patients were found to have been treated conservatively with anticholinergic medication. They conclude that “dysfunctional voiding symptoms after sling procedure should elicit a high degree of suspicion if pharmacotherapy is not successful in alleviating symptoms...Cystoscopy should be considered if the patient remains symptomatic despite pharmacotherapy.”

In one of the Nilsson studies, Dr. Nilsson describes four patients on “anticholinergics” (Int Urogynecol J 2008 Table 3). They conclude: “It is also encouraging to see that no late adverse effects of the polypropylene tape material was found and that erosion of the tape into

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<sup>245</sup> Karram, M.M., et al., *Complications and untoward effects of the tension-free vaginal tape procedure*, Ob & Gyn 2003, 101:929-32.

<sup>246</sup> de Tayrac, R., et al, *A prospective randomized trial comparing tension-free vaginal tape for surgical treatment of stress urinary incontinence*, Am J Obstet Gynecol 2004, 190:602-8.

<sup>247</sup> Deng D.Y., et al., *Presentation and management of major complications of midurethral slings: Are complications under reported*, Neurourology Urodynamics 2007, 26:46-52.

adjacent tissue did not occur.” However, this statement cannot be made for 4 patients who are on pharmacotherapy without a cystoscopy, which was not performed in the 11 year follow-up study. Dr. Raz’s review of the literature found multiple cases of urethral erosions in a large series with TVT.<sup>248</sup> There have also been multiple case reports attesting to the fact that urethral erosion does occur specifically with Gynecare TVT products.<sup>249</sup> To imply that urethral erosion does not occur is not giving physicians fair and balanced information about the true incidence of urethral erosions with TVT products.

Later, Nilsson publishes the 5 year follow-up of this cohort.<sup>250</sup> He describes the cohort: “a prospective open multicenter trial was conducted in the Nordic countries at the beginning of 1995. The short-term results were published in 1998.” This implies that these are the same patients as published in 1998. It is interesting or an incredible coincidence that the exact number of patients receiving 12 months of follow-up in the Medscand publication (90) was the exact number being described in the 5 year study. There is again no mention of the outcome of the other 41 patients from the original cohort. Another interesting detail in the 5 year study is that the original number of centers used for the study (6) was now down to 3, again without explanation. The 5 year report does describe the original patient with the wound infection but again fails to mention she had mesh excised, “1 case (1.1%) of infection of operating site was observed.”

In 2006, Dr. Nilsson published a different study on long term outcome of patients with

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<sup>248</sup> Karraam 2003, Hammad 2005.

<sup>249</sup> Sweat, S., et al, *Polypropylene Mesh Tape for Stress Urinary Incontinence: Complication of Urethral Erosion and Outlet Obstruction*, J Urology 2002, 168:144-146; Gerstenbluth, R.E., et al, *Simultaneous Urethral Erosion of Tension-Free Vaginal Tape and Woven Polyester Pubovaginal Sling*, J Urol. 2003, (2 Pt 1) 170:525-6; Vassallo, B.J., et al., *Management of iatrogenic Vaginal Constriction*, Am J Obstet Gynecol 2003, 102(3):512-20; Haferkamp, A., et al., *Urethral Erosion of Tension-Free Vaginal Tape*, J Urol 2002, 167(1): 250.

<sup>250</sup> Ulmsten data; Nilsson, Int Urogynecol J 2001.

TVT.<sup>251</sup> He describes his new patient population: “A multi-center study comprising only carefully selected primary cases revealed a promising cure rate of 85% after 5 years (reference his 5 year study) and 81% at 7 years.”<sup>252</sup> These two papers are the subject of many press releases and marketing brochures, but they never described that these were carefully selected patients. “To our knowledge, the long-term effect and effectiveness of the TVT procedure has not yet been studied in an unselected patient group. We earlier reported 16-month follow-up results of a general patient group referred to a tertiary medical unit and comprising primary, recurrent, mixed, and low pressure urethra cases. In the present study, we report the long-term results in the same above-mentioned group.” They describe a 3.1% mesh “visualized” rate, half of which needed surgical resection. These results, more representative of what one would see in a normal practice, is never mentioned in press releases or marketing documents.

Conversely, when Ethicon receives adverse information, it does not make it into the promotional pieces. Dr. AC Wang's abstract, “Tension-Free Vaginal Tape (TVT) for Urinary Stress Incontinence - A Preliminary Report” was used in the original 510k submission in October of 1997 as support for FDA clearance of the TVT.<sup>253</sup> However, when Dr. Wang reported that he had 25 cases of “failure of vaginal healing considered by him to be potential tape rejection...in each case the revision failed within 2 weeks, requiring further surgery to excise mesh and repair the vaginal wound,” this important information never made it into the marketing materials or press releases.<sup>254</sup>

The long-term follow-up data (Ulmsten/Nilsson data) used by Ethicon to promote the lack of risk of TVT is spurious at best. We have incomplete data on the original cohort, data

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<sup>251</sup> Kuuva, N., et al., *Long-term results of the tension-free vaginal tape operation in an unselected group of 129 stress incontinent women*, Acta Obstetrica Gynecologica Scandinavica 2006, 85:4 482-87.

<sup>252</sup> Nilsson, Obstet Gynecol 2004.

<sup>253</sup> ETH.MESH.00371551.

that is falsely reported, original sites that were excluded without explanation and a lead investigator who had a significant relationship and financial incentive to reach certain results with the data. This is the same data which is now used repeatedly in promotional and marketing materials sent to physicians.

**K. The Benefits of the TVT are Outweighed by the Severe, Debilitating and Life Changing Complications Associated with TVT**

It is my opinion, based on my training, experience and extensive review of the literature and Ethicon's internal documents that the benefits of the TVT are outweighed by the severe, debilitating and life changing complications associated with the medical device. It is clear that a substantial number of women who are implanted with the TVT have already and will continue to suffer chronic, debilitating erosions or pain, among other complications, and these life changing complications outweigh the benefits of the TVT, a device used to treat a quality of life issue.

This is especially true given that traditional surgeries like the Burch and pubovaginal slings are not associated with the frequency or extent of these life changing complications. The efficacy of the TVT is equivalent to the traditional surgeries like the Burch. Traditional surgeries are not associated with TVT mesh based complications like contraction and erosion, however, with clinically significant erosion. And, further, although traditional surgeries can cause symptoms such as pain following surgery, including dyspareunia, the risk, duration, extent and severity of chronic pain including dyspareunia following the TVT is much greater than with traditional surgeries, and of course those surgeries do not result in the often untreatable complications and symptoms that result from the TVT mesh.

There were reasonably feasible alternatives available to Ethicon for the treatment of

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<sup>254</sup> ETH.MESH.00409675.

patients in this case. For example, the Burch procedure would have been an appropriate treatment for the stress urinary incontinence. The Burch procedure eliminates the risks specifically associated with the old construction heavyweight mesh used in the TVT because the Burch procedure does not require the use of mesh. Another feasible alternative to the TVT would have included autologous fascia slings.

Moreover, in this case, because of the injuries suffered by the patient, and because of the manufacturing defect present in the mechanical cut mesh in this case, several additional feasible alternatives were available to Ethicon that would have been less dangerous. As I have testified in previous cases where women have suffered permanent debilitating injuries from TVT mesh products, these alternatives depend on the patient, patient's lifestyle, patient's medical history, and the injuries the patient suffers from. When patients are young and active at the time of surgery, like in this case, and when the mesh contains a manufacturing defect making the mesh especially prone to losing particles, fraying and deformation, like in this case, and because of injuries and risks from the TVT device, certain lighter weight, larger pore mesh resistant to fraying, deformation, shrinkage and particle loss both by design and by improved manufacturing, and include a less invasive implantation method than that used with the TVT would have been less dangerous and a feasible alternative.

In addition, based on Ethicon's internal documents, deposition testimony, and the medical literature, feasible alternatives would have included individually or collectively a lighter weight, larger pore mesh material. Indeed, Ethicon had lighter weight larger pore meshes that were less stiff and more compliant with patients' tissues that Ethicon marketed for use in the pelvis. A midurethral sling device which contained a shorter piece of mesh



and had arms consisting of suture like material would have also been a safer alternative.

Additionally, I continue to review internal Ethicon documents and the relevant body of medical literature on a continual basis. I also see women with chronic mesh complications on a continual basis. When I evaluate these women, whether it is in my practice or in a litigation setting, I see life-altering injuries that are related to the type of mesh these women were implanted with, the method in which the mesh was implanted, where the mesh was implanted, but also the patient's lifestyle and makeup. In many of these cases, where one option may be less dangerous for a certain patient, in another patient that same option may be more dangerous. This is because of the unique patient specific concerns that pelvic floor surgeons, like myself, encounter on a daily basis when evaluating medical treatment for specific patients. Indeed, Ethicon and the inventor of the TVT recognized this very concept.

Unfortunately, although there have been a large number of studies and publications involving the TVT over the years, the quality of most of the studies is not good, and the amount of bias included in the studies and publications adds to the limited value that the studies offer about long term, severe and debilitating complications like chronic pain and erosions associated with the TVT. The most recent Cochrane review of mid-urethral slings, Ogah (2011), concluded that most trials involving mid-urethral slings had short follow-up and the quality of evidence was variable such that the quality of evidence for the majority of trials was moderate with a minority having low-to-moderate evidence.<sup>255</sup> Few trials reported outcomes after 1 year and long term adverse effects had yet to be determined. There are only a handful of RCTs involving the TVT that are long term, and major and long term complications

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<sup>255</sup> Ohah, et. al., Minimally Invasive Synthetic Suburethral Sling Operations for Stress Urinary Incontinence in Women: A Short Version Cochrane Review. Neurology and Urodynamics 30:284-291 (2011).

would unlikely be picked up in these RCTs in part because they are designed with a primary endpoint of efficacy, not safety. The true incidence are more likely to be determined by registries or databases, but published registries do not track certain complications such as pain or dyspareunia, and have not been designed to monitor long term problems (Tamussino, 2001 and 2007; Kuuva 2002, Collinet, 2008, Dykorn 2010). This void in studying and presenting the true incidence and nature of long term and life altering complications, along with the biases inherent in many of the studies, and other factors, negates the value of the large majority of the studies, and as a result, other sources of data such as published case series are relevant and important to truly understand the nature of these complications. Ethicon's internal documents and data, which are not publically available, present a very different picture of the TVT than the information that has been shared with patients and physicians.

I have done an in-depth review and analysis of the studies, and am prepared to discuss the studies including the small number of studies that have tracked chronic pain, dyspareunia and erosions on a long term basis. The Abbott study is particularly noteworthy, however. Abbott (2014) described a series of 347 patients evaluated for mesh related complications from 2006 -2010. Approximately 50% had a sling only and an additional 26% had a sling and TVM mesh. The median time from placement to evaluation was 5.8 months with a range of 0 – 65.2. This would mean that many of these patients would not have been captured in registries or RCT's with one year or less follow-up. Also only 26% were seen by another facility before attending one of the study sites, meaning that at least  $\frac{3}{4}$  of these complications were not known to the implanting physician, again highlighting the limited utility of data at the primary site. The authors found 30% of patients had dyspareunia, 43% had erosion and 35% had pelvic

pain.<sup>256</sup> This study highlights the degree and severity of the complications that mesh slings like the TVT are causing and, importantly, that physicians in the real world simply do not have the information about the severity of the problem. This is why it is extremely important for manufacturers of slings like Ethicon to accurately and fully report the risks and complications associated with the mesh devices to doctors – something Ethicon simply has not done.

**L. It has been known since the launch of the TVT that the mesh can be difficult to remove, is susceptible to degradation, can rope, curl, deform, fray, and lose particles, and is a heavy weight mesh. However, Ethicon did not account for this facts in its dFMEA at the time of launch, and has failed to complete a proper risk analysis of these hazards**

Ethicon adopted revision 8 of the “Preventia” risk analysis prepared by Medscand AB for the TVT device as part of the TVT design history file.<sup>257</sup> This risk assessment was done on July 12, 2000, and omits numerous risks including that the mesh (1) can be difficult to remove, (2) is susceptible to degradation, (3) can rope, curl, deform (4) fray, and lose particles, and (5) is a heavy weight mesh. Ethicon does not have the previous versions of the risk assessments, revisions 1-7, which would include the version of the risk assessment performed prior to the launch of the TVT in late 1998, but it is reasonable to assume that if these risks had been identified in prior versions, they would still appear in revision 8 dated in July of 2000.<sup>258</sup> In April of 2002, Ethicon identified 11 risks that had been omitted from the Preventia revision 8 risk assessment. These risks include:

- Vaginal Extrusion
- Erosion/Urethral
- Perforation by Mesh
- Infection
- Vaginal Incision
- Urethral Tear

<sup>256</sup> Abbott, et. al., Evaluation and management of complications from synthetic mesh after pelvic reconstructive surgery: a multicenter study. American Journal of Obstetrics & Gynecology. (Feb. 2014).

<sup>257</sup> ETH.MESH.01317508.

<sup>258</sup> Deposition of Dan Smith, 06-04-2013 794:8-18. Mr. Smith testified that “no person at Ethicon.”

- Mesh Broken
- Torn Mesh
- Bent Needle
- Mesh Kinked(Twisted)
- Dull Needle

These are all risks that Ethicon knew or should have known at the time of launch of the TVT, and thus should have been assessed prior to launch. Because Ethicon failed to even identify these eleven risks, they also failed to assess the predicted and actual severity and frequency of these events, overall risk score, and actions needed to mitigate the risks of these failures. In addition, Ethicon also failed to identify and assess the other five risks discussed above at the time of launch 1998, or in 2002 when 11 new risks were identified, and still has not conducted a proper risk analysis to this day.

Ethicon clearly did not consider and analyze that TVT mesh (1) can be difficult to remove, (2) is susceptible to degradation, (3) can rope, curl, deform (4) fray, and lose particles, and (5) is a heavy weight mesh as potential failure modes. These were critical analyses in designing and marketing the TVT product and needed to be performed to conduct an appropriate risk analysis and mitigation strategy. There is no mention of these failure modes in the dFMEA in Ethicon's possession at launch, and there has been no proper analysis of these failure modes to this day. It is opinion that Ethicon has failed to meet the standard of care of a reasonable device manufacturer by failing to include these known risks associated with the TVT device on its risk assessments at launch, and has failed to properly assess these known risks to this day.

## **V. CONCLUSION.**

Ethicon has marketed and sold the TVT despite the fact that it contains numerous characteristics that make it unsuitable for implantation in a woman's vagina. These characteristics include the following: (1) degradation of the mesh; (2) chronic foreign

body reaction; (3) fraying, sharp edges and particle loss; (4) Infections and Bio-films; (5) roping and curling of the mesh; (6) loss of pore size with tension; (7) fibrotic bridging leading to scar plate formation and mesh encapsulation; and (8) shrinkage/contraction of the encapsulated mesh.

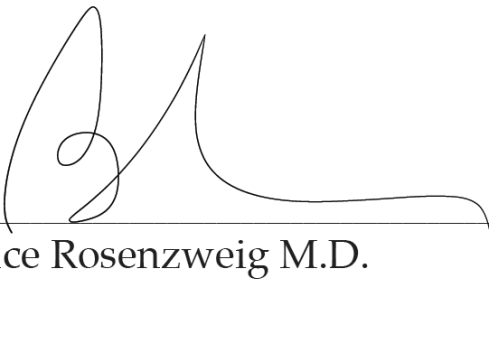
Not only does Ethicon sell a product which should never be put in the vagina, it failed to inform physicians and their patients about numerous risks associated with the product despite the fact that these risks were known before the product was launched. Ethicon has removed the ability of physicians to appropriately inform their patients of the risks and benefits of the TVT and made it impossible for women to consent to the procedure. In addition, despite having knowledge to the contrary, Ethicon never informed physicians and their patients that the TVT could be toxic to their bodies. Finally, while keeping this information from women, Ethicon marketed its product with promotional pieces that did not disclose key conflict of interest information or the true complication rates of its products.

As a result of these failures as fully set forth in this report, the TVT has caused and will continue to cause a multitude of injuries in women, including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, nerve injury, recurrence, worsening incontinence, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others.

All opinions I have are to a reasonable degree of medical certainty. I understand discovery is still ongoing in this case and I reserve my right to amend my opinions if further information is provided in any form including, but not limited to, corporate documents,

depositions and expert reports of both Plaintiff and Defense experts. I have also reviewed the opinions of Dr. Uwe Klinge, Dr. Muhl, Dr. Vladimir Iakovlev and Dr. Elliott and incorporate those opinions herein.

Signed this 24th day of August, 2015.

X   
Bruce Rosenzweig M.D.